LINGO binding molecules and Pharmaceutical Use Thereof

The present invention relates to LINGO binding molecules, such as for example monoclonal antibodies or Fab fragments thereof, and the use of such binding molecules for treating patients with injuries to their central nervous system.

Background of the invention

Functional recovery following injury to the central nervous system (CNS) of adult higher vertebrates is exceptionally limited, resulting in persistent neurological deficits such as loss of limb movement and sensation. As yet, there is a lack of an effective therapy to treat humans with CNS injuries such as spinal cord injury (SCI) and brain cortical injury. Although adult CNS neurons generally survive axotomy, axonal regeneration is transitory and only occurs over a confined area, hence retarding the re-formation of functionally-relevant synaptic contacts. Furthermore, the plastic capacity of the adult CNS is also restricted, thus hindering the re-organisation of uninjured pathways to functionally compensate for those ablated by the injury. Paradoxically, axotomised axons in the peripheral nervous system (PNS) have a high capacity to regenerate over long distances and frequently establish functionally-meaningful connections (Schwab (2004) Curr Opin Neurobiol 14,118-124). This restriction in axonal regeneration/plasticity is in part due to the expression on myelinating oligodendrocytes of several proteins that have been shown to be potent inhibitors of neurite outgrowth, namely Nogo-A (Chen et al. (2000) Nature 403, 434-439; GrandPre et al. (2000) Nature 403, 439-444; Prinjha et al. (2000) Nature 403, 383-384), myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp) (McKerracher et al. (1994) Neuron 13, 805-811; Wang et al. (2002) Nature 417:941-944) (Fig. 1A).

Nogo-A contains multiple neurite outgrowth inhibitory domains exposed on the surface of oligodendrocytes: two are located within the amino-terminal region (amino-Nogo-A) and one in the C-terminal region (Nogo-66) (Oertle et al. (2003) J Neurosci 23, 5393-5406). Nogo-66 binds and signals through a glycosyl-phosphatidylinositol (GPI)-anchored leucine-rich repeat (LRR)-containing receptor on the neuronal surface known as the Nogo-66 receptor (NgR) (Fournier et al. (2001) Nature 409, 341-346). Although structurally unrelated, MAG and OMgp also bind and signal through NgR (Domeniconi et al. (2002) Neuron 35, 283-290; Liu

et al. (2002) Science 297, 1190-1193; Wang et al. (2002) Nature 417:941-944). Signaling through NgR leads to the activation of the small GTPase RhoA which in turn activates Rho-associated kinase (ROCK) leading to a rigidification of the actin cytoskeleton and inhibition of axonal extension (Niederöst et al. (2002) J Neurosci 22, 10368-10376; Schweigreiter et al. (2004) Mol Cell Neurosci 27:163-174). All three ligands bind within the LRR region of NgR and have partially over-lapping binding sites (Fournier et al. (2002) J Neurosci 22, 8876-8883; Liu et al. (2002) Science 297, 1190-1193; Wang et al. (2002) Nature 417:941-944; Barton et al. (2003) EMBO J 22, 3291-3302). The receptor(s) for the inhibitory domains within amino-Nogo-A are unknown but have been shown to be distinct from NgR (Schweigreiter et al. (2004) Mol Cell Neurosci 27:163-174). MAG has also been found to signal through a close homologue of NgR known as NgR2 (Pignot et al. (2003) J Neurochem 85, 717-728; Venkatesh et al. (2005) J Neurosci 25, 808-822).

As NgR lacks a cytoplasmic domain, it utilizes several transmembrane proteins for signal transduction, namely the low affinity neurotrophin receptor $p75^{NTR}$, TROY (a.k.a. TAJ) and LINGO-1 (LRR and Ig domain-containing, Nogo receptor-interacting protein a.k.a LRRN6A or LERN1) (Wang et al. (2002) Nature 420, 74-78; Carim-Todd et al. (2003) Eur J Neurosci 18, 3167-3182; Mi et al. (2004) Nat Neurosci 7, 221-228; Park et al. (2005) Neuron 45:345-351; Shao et al. (2005) Neuron 45, 353-359). TROY and $p75^{NTR}$ can functionally replace each other in the NgR receptor complex, whereas the presence of LINGO-1 is an absolute prerequisite for signaling to occur. The NgR receptor complex is therefore seen as a ternary complex comprising NgR as the ligand binding subunit and LINGO-1 as the common signal transducing subunit acting in concert with either $p75^{NTR}$ or TROY.

LINGO-1 is a single transmembrane protein expressed exclusively within the CNS predominantly on neurons and oligodendrocytes .The expression of LINGO-1 peaks in the early postnatal period and is up-regulated in the adult spinal cord upon injury. The ectodomain of LINGO-1 contains twelve tandem LRRs flanked by N- and C-terminal subdomains followed by a basic region and an Ig domain (Fig. 1B). Given that an AP fusion of the LINGO-1 ectodomain bound to COS-7 cells expressing NgR or $p75^{NTR}$ or both and, similarly, LINGO-1 co-precipitated with NgR or $p75^{NTR}$ in cells expressing all three proteins, LINGO-1 most likely forms a ternary complex with NgR and $p75^{NTR}$ by interacting with both simultaneously.

In addition to being expressed on neurons, LINGO-1 is also expressed in oligodendrocytes in the adult CNS (Mi et al. (2005) Nat Neurosci 8, 745-751). Inhibiting LINGO-1 signaling in oligodendrocyte cultures by either treatment with LINGO-1-Fc, down-regulation of the protein with RNAi or over-expression of DN-LINGO-1 augmented the differentiation of OPCs to myelinating oligodendrocytes. Furthermore, genetic ablation of LINGO-1 in mice increased the number of mature oligodendrocytes and, correspondingly, myelinated axons in the spinal cord. Inhibition of LINGO-1 signaling reduced the activation of RhoA and increased the activity of Fyn kinase, both of which are reported to promote oligodendrocyte differentiation, although the actual ligands/interactions responsible for activating LINGO-1 signaling have yet to be exemplified. This has led to the conclusion the LINGO-1 is a negative regulator of myelination.

Multiple Sclerosis (MS) is a chronic inflammatory disease of the CNS characterised by demyelination and axonal degeneration leading to multiple neurological deficits. Although remyelination of axons can occur early in the disease, at some point remyelination fails completely leading to accelerated axonal degeneration and irreversible damage. Remyelination most likely arises from the differentiation of adult oligodendrocyte precursor cells (OPCs) which migrate to the margins of active lesions. As LINGO-1 negatively regulates myelination, blockade of LINGO-1 may augment remyelination, attenuate axonal degeneration, promote axonal regeneration and thus attenuate, halt or even reverse the progress of demyelinating diseases such as MS.

Blockade of LINGO-1 has also been shown to improve the survival of dopaminergic neurons and reduce behavioural abnormalities in rodent models of Parkinson's disease (Inoue et al. (2007) Proc Natl Acad Sci USA 104, 14430-14435).

Summary of the invention

It has now surprisingly been found that novel monoclonal human antibodies against LINGO-1 (known as antibody 4784, and antibody 4785 hereafter) significantly inhibit the association of LINGO-1 with NgR and significantly attenuate the neurite outgrowth inhibitory activity of adult rat spinal cord myelin at sub-nM concentrations in vitro. In addition, the said antibodies significantly increase the differentiation of primary oligodendrocytes in vitro and have been shown to significantly downregulate cell surface LINGO-1 in living cells. Treatment with

these antibodies is expected to increase axonal regeneration/plasticity and improve functional recovery following acute CNS injuries such as SCI and brain cortical injury. Furthermore, blocking LINGO-1 signaling using the said antibodies in oligodendroglial cells has the potential to augment the remyelination of axons in demyelinating diseases such as MS leading to an attenuation of disease progression. In concert, inhibiting LINGO-1 signaling in neurons with the said antibodies can be expected to improve axonal regeneration and neuroplasticity and promote the recovery of neurological function lost during the course of the disease. Finally, blockade of LINGO-1 with the said antibodies can be expected to attenuate the pathogenesis of Parkinson's disease.

Furthermore, the invention provides binding molecules which bind to specific epitopes on LINGO-1.

The antibodies have sub-nM K_Ds against the rat, cynomolgus monkey and human LINGO-1 ectodomain, significantly attenuate the neurite outgrowth inhibitory activity of adult rat spinal cord myelin at sub-nM concentrations and significantly increase oligodendrocyte differentiation in vitro. Moreover, it is now possible to construct other LINGO-1 binding molecules having the same variable regions as said antibodies.

Detailed description of the invention

Accordingly, the invention provides binding molecules to a particular region or epitope of LINGO-1 (hereinafter referred to as "the binding molecules of the invention" or simply "binding molecules").

The binding molecules of the invention bind the mature ectodomain (residues 34-550) of rat LINGO-1 (SEQ ID NO: 1), cynomolgus monkey LINGO-1 (SEQ ID NO: 2) and human LINGO-1 (SEQ ID NO: 3) with a dissociation constant (K_D) < 1000nM, more preferably with a K_D < 100 nM, most preferably with a K_D < 10 nM. The binding reaction may be shown by standard methods (qualitative assays) including, for example, the FACS method described in Examples. In addition, the binding to rat, cynomolgus monkey and human LINGO-1, and

also the efficiency, may be shown in a neurite outgrowth assay and oligodendrocyte assay as described below.
Thus, in a further preferred embodiment the binding molecules (at a concentration of 100 nM, preferably 10 nM, more preferably at 1 nM even more preferably at 0.1 nM) increase the mean neurite length per cell of rat cerebellar granule cells grown on a substrate of adult rat spinal cord myelin by at least 20%, preferably 50%, most preferred 60% compared to the mean neurite length per cell of rat cerebellar granule cells which are treated with a control antibody that does not bind to the rat, cynomolgous monkey and human LINGO-1 ectodomain.

By using peptide microarrays, the specific epitope to which the binding molecules of the invention bind is determined according to methods well known in the art. Consequently, in another embodiment the invention provides binding molecules which bind to at least one of the LINGO-1 epitopes as defined by SEQ ID NO: 46-51. SEQ ID NO: 46: KIVILLDYMFQD, SEQ ID NO: 47: AIRDYSFKRLYR, SEQ ID NO: 48: LKVLEISHWPYL, SEQ ID NO: 49: NLTAVPYLAVRHLVY, SEQ ID NO: 50: YFTCRRARI, or SEQ ID NO: 51: DVLLPNYFTCRRARI.

In another embodiment, the binding molecules of the invention comprises one or more, of the following CDR sequences, e.g. all of the Antibody 4784 or all of the Antibody 4785 sequences mentioned there:

SEQ ID NO: 12
(Antibody 4784 CDR-H1)
SSGVGVG

SEQ ID NO: 13
(Antibody 4784 CDR-H2)
HIGSDDDKYYSTSLKT

SEQ ID NO: 14
(Antibody 4784 CDR-H3)

NQQYGDGYPGYFDY

SEQ ID NO: 15
(Antibody 4784 CDR-L1)
SGDNIGNYYVY

SEQ ID NO: 16
(Antibody 4784 CDR-L2)
EDTNRPS

SEQ ID NO: 17
(Antibody 4784 CDR-L3)
QSYDNLHEQV

SEQ ID NO: 18
(Antibody 4785 CDR'-H1)
DNSAAWS

SEQ ID NO: 19
(Antibody 4785 CDR'-H2)
LIYLRSKWDNDYAVSVKS

SEQ ID NO: 20
(Antibody 4785 CDR'-H3)
TGRADEFDV

SEQ ID NO: 21
(Antibody 4785 CDR'-L1)
SGSSSNIGNNYVS

SEQ ID NO: 22
(Antibody 4785 CDR'-L2)
RNSKRPS

SEQ ID NO: 23
(Antibody 4785 CDR'-L3)
STYDTFSIV

More preferably, the binding molecules comprise one or more of the sequences given above for Antibody 4784 with the SEQ ID NO: 12, 13, 14, 15, 16 and/or 17; or for Antibody 4785 with the SEQ ID NO: 18, 19, 20, 21, 22 and/or 23.

Those skilled in the art understand that changes can be made to 4784 or 4785 which, though they change several, more preferably one or more amino acids, preferably up to three, e.g. one or two, of the SDRs given above, especially in one or more or all of them, e.g. one or two of them, or provide alternative post-translational modification of product formats, result in a therapeutic agent demonstrating the same or substantially similar anti-Lingo-1 binding behaviour.

In another embodiment the binding molecules of the invention comprises at least one antigen binding site chosen from the group consisting of; a sequence which is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% homologous to SEQ ID NO: 5 or SEQ ID NO: 7, and;
a sequence which is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% homologous to SEQ ID NO: 4 or SEQ ID NO: 6, or a direct equivalent thereof.

In one embodiment, the binding molecule comprises at least one binding site chosen from the group consisting of SEQ ID NO: 5 or SEQ ID NO: 7, and;
SEQ ID NO: 4 or SEQ ID NO: 6.

The invention further provides a binding molecule which comprises a first sequence which is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% homologous to SEQ ID NO: 5, and a second sequence which is at least 50% at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% homologous to SEQ ID NO: 4, or a direct equivalent thereof.

The invention further provides a binding molecule which comprises a first sequence which is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% homologous to SEQ ID NO: 7, and a second sequence which is at least 50% at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% homologous to SEQ ID NO: 6, or a direct equivalent thereof.

In one embodiment, the invention provides a binding molecule according to claims 1 to 7 which comprises at least

a) one immunoglobulin heavy chain or fragment thereof which comprises
(i) a variable domain comprising SEQ ID NO: 5 or SEQ ID NO: 7, and
(ii) the constant part or fragment thereof of a human heavy chain; and
b) one immunoglobulin light chain or fragment thereof which comprises
(i) a variable domain comprising SEQ ID NO: 4 or SEQ ID NO: 6, and
(ii) the constant part or fragment thereof of a human light chain; or
direct equivalents thereof; e.g. two or three of each of the chains given under a) or b).

The sequences may be at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% homologous to SEQ ID NO: 4-7. The important factor is that such variants retain the binding capabilities to LINGO-1, the disinhibitory effect (especially the ability to attenuate the neurite outgrowth inhibitory activity of adult rat spinal cord myelin at sub-nM concentrations), and/or to improve the funcrtional recovery of SCI (especially in a rat model), in each case preferably as described in the Examples or the remaining description.

In one embodiment, the invention provides a binding molecule which is an antibody comprising one or more of the sequences according to SEQ ID NO: 4-7 or SEQ ID NO: 12-23, or a fragment thereof, or a direct equivalent thereof.

In a further embodiment, the binding molecule, as an antibody, has a constant part or fragment thereof of the human heavy chain of the γ4 type and the constant part or fragment thereof of the human light chain is of the λ type.

In a further embodiment, the binding molecule, as an antibody, has a constant part or fragment thereof of the human heavy chain of the γ4 type and the constant part or fragment thereof of the human light chain is of the κ type.

In a further embodiment, the binding molecule is a human or chimeric or humanized monoclonal antibody.

In a further embodiment, the binding molecule is a humaneered antibody.

The invention also provides a polynucleotide encoding a binding molecule as defined above.

The polynucleotide may be chosen from the group consisting of SEQ ID NO: 8 and SEQ ID NO: 9; or from the group consisting of SEQ ID NO: 10 and SEQ ID NO: 11.

The invention also provides an expression vector comprising one or more polynucleotides according to SEQ ID NO:8-11.

Furthermore, the invention provides an expression system comprising a polynucleotide according to SEQ ID NO:8-11, wherein said expression system or part thereof is capable of producing a binding molecule as set out above, when said expression system or part thereof is present in a compatible host cell. The invention also provides an isolated host cell which comprises such an expression system.

The invention also provides the use of a binding molecule as set out above, as a medicament.

The invention also provides the use of a binding molecule as set out above in the preparation of a medicament for the treatment of a CNS injury.

The invention also provides a pharmaceutical composition comprising a binding molecule as set out above together with at least one pharmaceutically acceptable carrier or diluent.

Furthermore, the invention provides a method of treatment of diseases associated with the promotion of axonal regeneration/plasticity comprising administering to a subject in need of such treatment an effective amount of a binding molecule as set out above.

The invention also provides a method of treatment of diseases associated with the promotion of axonal regeneration/plasticity comprising administering to a subject in need of such treatment an effective amount of a binding molecule according to any one of claims 1 to 10.

When the antigen binding site comprises both the first and second domains, these may be located on the same polypeptide molecule or, preferably, each domain may be on a different chain, the first domain being part of an immunoglobulin heavy chain or fragment thereof and the second domain being part of an immunoglobulin light chain or fragment thereof.

Examples of binding molecules of the invention include antibodies as produced by phage display and human or chimeric humanized antibodies, or furter humaneered antibodies, or any fragment thereof, e.g. F(ab')2; and Fab fragments, as well as single chain or single domain antibodies. The term "antibody" is meant to include such binding molecules.

A single chain antibody consists of the variable domains of an antibody heavy and light chains covalently bound by a peptide linker usually consisting of from 10 to 30 amino acids, preferably from 15 to 25 amino acids. Therefore, such a structure does not include the constant part of the heavy and light chains and it is believed that the small peptide spacer should be less antigenic than a whole constant part. By "chimeric antibody" is meant an

antibody in which the constant regions of heavy or light chains or both are of human origin while the variable domains of both heavy and light chains are of non- human (e.g. murine) origin. By "humanized antibody" is meant an antibody in which the hypervariable regions (CDRs) are of non-human (e.g. murine) origin, while all or substantially all the other parts of the immunoglobulin e.g. the constant regions and the highly conserved parts of the variable domains, i.e. the framework regions, are of human origin. A humanized antibody may however retain a few amino acids of the murine sequence in the parts of the framework regions adjacent to the hypervariable regions.

Hypervariable regions may be associated with any kind of framework regions, preferably of murine or human origin. Suitable framework regions are described in "Sequences of proteins of immunological interest" (Kabat E.A. et al, US department of health and human services, Public health service, National Institute of Health, preferably incorporated herein, especially with regard to the framework regions, by reference). Preferably the constant part of a human heavy chain of the binding molecules may be of the $\gamma 4$ type, including subtypes, preferably the constant part of a human light chain may be of the κ or λ type, more preferably of the λ type.

A naturally occurring "antibody" is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain, C_L. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors,

including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system.

The term "antigen-binding portion" of an antibody (or simply "antigen portion"), as used herein, refers to full length or one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., LINGO-1 and/or LINGO-2). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and CH1 domains; a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the V_H and CH1 domains; a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody; a dAb fragment (Ward et al., 1989 Nature 341:544-546), which consists of a V_H domain; and an isolated complementarity determining region (CDR).

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition (that is, that are identical because they are produced by one type of immune cell that are all clones of a single parent cell). A monoclonal antibody composition displays an (essentially) single binding specificity and affinity for a particular epitope.

The term "human antibody", as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, e.g., human germline sequences, or mutated versions of human germline sequences. The human antibodies of the invention may include amino acid residues not encoded by human sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The term "human monoclonal antibody" refers to antibodies displaying an (essentially) single binding specificity which have variable regions in which both the framework and CDR regions are derived from human sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.
The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, antibodies isolated from a recombinant, combinatorial human antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of all or a portion of a human immunoglobulin gene, sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire in vivo.

As used herein, "isotype" refers to the antibody class (e.g., IgM, IgE, IgG such as IgG1 or IgG4) that is provided by the heavy chain constant region genes.

As used herein, the term "Affinity" refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity.

The term "K_D", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of K_d to K_a (association rate to dissociation rate) (i.e. K_d/K_a) and is

expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. A method for determining the K_D of an antibody is by using surface plasmon resonance, or using a biosensor system such as a Biacore® system.

A binding molecule according to the invention is preferably an "isolated antibody", which, as used herein, refers to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds LINGO-1, LINGO-2 or LINGO-1 and LINGO-2 is substantially free of antibodies that specifically bind antigens other than those mentioned). An isolated antibody that specifically binds may, however, have cross-reactivity to other antigens, such as LINGO-1 or LINGO-2 molecules from other species. Moreover, an isolated antibody is preferably substantially free of other cellular material and/or chemicals.

The invention also provides a binding molecule of the invention which may be selected from a single chain binding molecule which comprises an antigen binding site (especially with the CDRs described above for Antibody 4784) of antibody 4784 comprising

a) a first domain comprising the variable sequence of the heavy chain having the amino acid sequence (SEQ ID NO: 5)
b) a second domain comprising the variable sequence of the light chain having the amino acid sequence (SEQ ID NO: 4)
c) a peptide linker which is bound either to the N- terminal extremity of the first domain and to the C-terminal extremity of the second domain or to the C-terminal extremity of the first domain and to the N-terminal extremity of second domain;

or direct equivalents thereof.

A binding molecule of the invention may be selected from a single chain binding molecule which comprises an antigen binding site (especially with the CDRs described above for Antibody 4785) of antibody 4785 comprising

a) a first domain comprising the variable sequence of the heavy chain having the amino acid sequence (SEQ ID NO: 7)
b) a second domain comprising the variable sequence of the light chain having the amino acid sequence (SEQ ID NO: 6)

c) a peptide linker which is bound either to the N- terminal extremity of the first domain and to the C-terminal extremity of the second domain or to the C-terminal extremity of the first domain and to the N-terminal extremity of second domain;

or direct equivalents thereof.

As it is well known, minor changes in an amino acid sequence such as deletion, addition or substitution of one or several amino acids may lead to an allelic form of the original protein which has substantially identical properties. Thus, by the term "direct equivalents thereof" is meant either any single domain binding molecule of the invention (molecule X)

(i) in which the variable region of the binding molecule (e.g. SEQ ID NO: 4, 5, 6 or 7) is at least 50 or 80% homologous, preferably at least 90% homologous, more preferably at least 95, 96, 97, 98, 99% homologous to the equivalent variable regions of the light and heavy chains comprising the direct equivalents of SEQ ID NO: 4 and SEQ ID NO: 5, respectively or light and heavy chains comprising the direct equivalents of SEQ ID NO: 6 and SEQ ID NO: 7, respectively).

(ii) which is capable of binding to the ectodomain (residues 34-550) of rat LINGO-1 (SEQ ID NO: 1), cynomolgus monkey LINGO-1 (SEQ ID NO: 2) and human LINGO-1 (SEQ ID NO: 3), preferably with a dissociation constant (K_D) < 1000nM, more preferably with a K_D < 100 nM, most preferably with a K_D < 10 nM, or any binding molecule of the invention having at least two domains per binding site (molecule X').

Thus further embodiments of the inventions are for example a binding molecule which is capable of binding to the ectodomain of rat, cynomolgus monkey and/or human LINGO-1 with a dissociation constant < 1000nM and comprises at least one antigen binding site, said antigen binding site comprising in sequence the variable region which is at least 50%, preferably 80, 90, 95, 96, 97, 98, 99% homologous to the equivalent variable regions of the light and heavy chains of 4784 (SEQ ID NO: 4 and SEQ ID NO: 5, respectively) or light and heavy chains of 4785 (SEQ ID NO: 6 and SEQ ID NO: 7, respectively).

In another embodiment, the binding molecule comprises at least one amino acid sequence chosen from the group consisting of SEQ ID NO: 12-23, or a sequence which is at least 50%, preferably 80, 90, 95, 96, 97, 98, 99% homologous to these sequences.

This dissociation constant may be conveniently tested in various assays including, for example, the FACS method described in the examples. In addition, the binding and functional effect of the binding molecules may be shown in a bioassay, e.g. the neurite outgrowth assay as described below.

The constant part of a human heavy chain may be of the γ1; γ2; γ3; γ4; α1; α2; δ or ε type, preferably of the γ type, more preferably of the γ4 type, whereas the constant part of a human light chain may be of the κ or λ type (which includes the λ1; λ2; and λ3 subtypes) but is preferably of the λ type. The amino acid sequence of all these constant parts are given in Kabat et al (Supra).

Conjugates of the binding molecules of the invention, e. g. enzyme or toxin or radioisotope conjugates, are also included within the scope of the invention.

"Polypeptide", if not otherwise specified herein, includes any peptide or protein comprising amino acids joined to each other by peptide bonds, having an amino acid sequence starting at the N-terminal extremity and ending at the C-terminal extremity. Preferably, the polypeptide of the present invention is a monoclonal antibody, more preferred is a chimeric (also called V-grafted) or humanised (also called CDR-grafted) monoclonal antibody. The humanised (CDR-grafted) monoclonal antibody may or may not include further mutations introduced into the framework (FR) sequences of the acceptor antibody.

A functional derivative of a polypeptide as used herein includes a molecule having a qualitative biological activity in common with a polypeptide to the present invention, i.e. having the ability to bind to the ectodomain of rat, cynomolgus monkey and human LINGO-1.

A functional derivative includes fragments and peptide analogs of a polypeptide according to the present invention. It also includes the term "direct derivatives".

Fragments comprise regions within the sequence of a polypeptide according to the present invention, e.g. of a specified sequence. Fragments of binding molecules, especially of

antibodies, are functional fragments, i.e. they comprise at least one portion capable of binding to LINGO-1 and/or LINGO-2, especially to at least one of the epitopes given by SEQ ID NO: 46, 47, 48, 49, 50 and 51, preferably with the binding affinities (K_D) mentioned above or in the Examples, especially as being preferred.

The term "derivative" is used to define amino acid sequence variants, and covalent modifications of a polypeptide according to the present invention. e.g. of a specified sequence. The functional derivatives of a polypeptide according to the present invention, e.g. of a specified sequence, e.g. of the hypervariable region of the light and the heavy chain, preferably have at least about 65%, more preferably at least about 75%, even more preferably at least about 85%, most preferably at least about 95, 96, 97, 98, 99% overall sequence homology with the amino acid sequence of a polypeptide according to the present invention, e.g. of a specified sequence, and substantially retain the ability to bind the ectodomain of rat, cynomolgus monkey and human LINGO-1 (and optionally in addition to LINGO-2).

The term "covalent modification" includes modifications of a polypeptide according to the present invention, e.g. of a specified sequence; or a fragment thereof with an organic proteinaceous or non-proteinaceous derivatizing agent, fusions to heterologous polypeptide sequences, and post-translational modifications. Covalent modified polypeptides, e.g. of a specified sequence, still have the ability to bind to the ectodomain of rat, cynomolgus monkey and human LINGO-1. Covalent modifications are traditionally introduced by reacting targeted amino acid residues with an organic derivatizing agent that is capable of reacting with selected sides or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deaminated under mildly acidic conditions. Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl, tyrosine or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains, see e.g. T. E. Creighton, Proteins: Structure and Molecular

Properties, W. H. Freeman & Co., San Francisco, pp. 79-86 (1983). Covalent modifications e.g. include fusion proteins comprising a polypeptide according to the present invention, e.g. of a specified sequence and their amino acid sequence variants, such as immunoadhesins, and N-terminal fusions to heterologous signal sequences.

"Homology" (or "identity) with respect to a native polypeptide and its functional derivative is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues of a corresponding native polypeptide, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology, and not considering any conservative substitutions as part of the sequence identity. Neither N- or C-terminal extensions nor insertions shall be construed as reducing identity or homology. Methods and computer programs for the alignment are well known.

Preferably, as used herein, the percent homology between two amino acid sequences or two nucleotide sequences is equivalent to the percent identity between the two sequences. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i. e., % homology = # of identical positions/total # of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below:

The percent identity between two amino acid sequences can be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:11-17, 1988) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol, Biol. 48:444-453, 1970) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

Additionally or alternatively, the protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for

example, identify related sequences. Such searches can be performed using the XBLAST program (version 2.0) of Altschul, et al., 1990 J.Mol. Biol. 215:403-10. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the antibody molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., 1997 Nucleic Acids Res. 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See http:www.ncbi.nhn.nih.gov.

"Amino acid(s)" refer to all naturally occurring L-α-amino acids, e.g. and including D-amino acids. The amino acids are identified by either the well known single-letter or three-letter designations.

The term "amino acid sequence variant" refers to molecules with some differences in their amino acid sequences as compared to a polypeptide according to the present invention, e.g. of a specified sequence. Amino acid sequence variants of a polypeptide according to the present invention, e.g. of a specified sequence, still have the ability to bind to the ectodomain of rat, cynomolgus monkey and human LINGO-1. Substitutional variants are those that have at least one amino acid residue removed and a different amino acid inserted in its place at the same position in a polypeptide according to the present invention, e.g. of a specified sequence. These substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more, e.g. 1 to 10, preferably 1 to 5, more preferably 1 to 3, amino acids have been substituted in the same molecule. Insertional variants are those with one or more, e.g. 1 to 100, such as 1 to 10, amino acids inserted immediately adjacent to an amino acid at a particular position in a polypeptide according to the present invention, e.g. of a specified sequence. Immediately adjacent to an amino acid means connected to either the α-carboxy or α-amino functional group of the amino acid. Deletional variants are those with one or more, e.g. 1 to 100, such as 1 to 10 or 1 to 5, amino acids in a polypeptide according to the present invention, e.g. of a specified sequence, removed. Ordinarily, deletional variants will have one or two amino acids deleted in a particular region of the molecule.

A binding molecule of the invention may be produced by recombinant DNA techniques. In view of this, one or more DNA molecules encoding the binding molecule must be constructed, placed under appropriate control sequences and transferred into a suitable host organism for expression.

In a very general manner, there are accordingly provided

(i) DNA molecules encoding a single domain binding molecule of the invention, a single chain binding molecule of the invention, a heavy or light chain or fragments thereof of a binding molecule of the invention; and

(ii) the use of the DNA molecules of the invention for the production of a binding molecule of the invention by recombinant means.

The present state of the art is such that the skilled person will be able to synthesize the DNA molecules of the invention given the information provided herein i.e. the amino acid sequences of the hypervariable regions and the DNA sequences coding for them. A method for constructing a variable domain gene is for example described in EP 239 400 (preferably incorporated herein by reference, especially regarding the methods for constructing a variable domain gene) and may be briefly summarized as follows: A gene encoding a variable domain of a monoclonal antibody of whatever specificity is cloned. The DNA segments encoding the framework and hypervariable regions are determined and the DNA segments encoding the hypervariable regions are removed so that the DNA segments encoding the framework regions are fused together with suitable restriction sites at the junctions. The restriction sites may be generated at the appropriate positions by mutagenesis of the DNA molecule by standard procedures. Double stranded synthetic variable region cassettes are prepared by DNA synthesis according to the sequences given above. These cassettes are provided with sticky ends so that they can be ligated at the junctions to the framework by standard protocol for achieving a DNA molecule encoding an immunoglobulin variable domain.

Furthermore, it is not necessary to have access to the mRNA from a producing hybridoma cell line in order to obtain a DNA construct coding for the monoclonal antibodies of the invention. Thus, PCT application W0 90/07861 (preferably incorporated herein by reference,

especially with regard to the production of monoclonal antibodies) gives full instructions for the production of a monoclonal antibody by recombinant DNA techniques given only written information as to the nucleotide sequence of the gene.

The method comprises the synthesis of a number of oligonucleotides, their amplification by the PCR method, and their splicing to give the desired DNA sequence.

Expression vectors comprising a suitable promoter or genes encoding heavy and light chain constant parts are publicly available. Thus, once a DNA molecule of the invention is prepared it may be conveniently transferred in an appropriate expression vector.

DNA molecules encoding single chain antibodies may also be prepared by standard methods, for example, as described in W0 88/1649 (preferably incorporated herein by reference, especially with regard to the DNA molecules encoding single chain antibodies).

In a particular embodiment of the invention, the recombinant means for the production of some of the binding molecules of the invention includes first and second DNA constructs as described below:

The first DNA construct encodes a heavy chain or fragment thereof and comprises

a) a first part which encodes the variable domain of the heavy chain of either antibody 4784, DNA-4784 V_H (SEQ ID NO: 8), or antibody 4785, DNA-4785 V_H (SEQ ID NO: 9); this first part starting with a codon encoding the first amino acid of the variable domain and ending with a codon encoding the last amino acid of the variable domain, and
b) a second part encoding a heavy chain constant part or fragment thereof which starts with a codon encoding the first amino acid of the constant part of the heavy chain and ends with a codon encoding the last amino acid of the constant part or fragment thereof, followed by a non-sense codon.

Preferably, the second part encodes the constant part of a human heavy chain, more preferably the constant part of the human γ4 chain. This second part may be a DNA fragment of genomic origin (comprising introns) or a cDNA fragment (without introns).

The second DNA construct encodes a light chain or fragment thereof and comprises

a) a first part which encodes the variable domain of the light chain of either antibody 4784, DNA-4784 V_L (SEQ ID NO: 10), or antibody 4785, DNA-4785 V_L (SEQ ID NO: 11); this first part starting with a codon encoding the first amino acid of the variable domain and ending with a codon encoding the last amino acid of the variable domain, and

b) a second part encoding a light chain constant part or fragment thereof which starts with a codon encoding the first amino acid of the constant part of the light chain and ends with a codon encoding the last amino acid of the constant part or fragment thereof followed by a non-sense codon.

Preferably, the second part encodes the constant part of a human light chain, more preferably the constant part of the human κ chain.

Each of the DNA constructs are placed under the control of suitable control sequences, in particular under the control of a suitable promoter. Any kind of promoter may be used, provided that it is adapted to the host organism in which the DNA constructs will be transferred for expression. However, if expression is to take place in a mammalian cell, it is particularly preferred to use the promoter of an immunoglobulin gene.

The desired antibody may be produced in a cell culture or in a transgenic animal. A suitable transgenic animal may be obtained according to standard methods which include micro injecting into eggs the first and second DNA constructs placed under suitable control sequences transferring the so prepared eggs into appropriate pseudo- pregnant females and selecting a descendant expressing the desired antibody.

When the antibody chains have to be produced in a cell culture, the DNA constructs must first be inserted into either a single expression vector or into two separate but compatible expression vectors, the latter possibility being preferred.

Accordingly, the invention also provides an expression vector able to replicate in a prokaryotic or eukaryotic cell line which comprises at least one of the DNA constructs above described.

Each expression vector containing a DNA construct is then transferred into a suitable host organism. When the DNA constructs are separately inserted on two expression vectors, they may be transferred separately, i.e. one type of vector per cell, or co- transferred, this latter possibility being preferred. A suitable host organism may be a bacterium, a yeast or a mammalian cell line, this latter being preferred. More preferably, the mammalian cell line is of lymphoid origin e.g. a myeloma, hybridoma or a normal immortalized B-cell, but does not express any endogeneous antibody heavy or light chain.

It is also preferred that the host organism contains a large number of copies of the vectors per cell. If the host organism is a mammalian cell line, this desirable goal may be reached by amplifying the number of copies according to standard methods. Amplification methods usually consist of selecting for increased resistance to a drug, said resistance being encoded by the expression vector.

In another aspect of the invention, there is provided a process for producing a multi-chain binding molecule of the invention, which comprises (i) culturing an organism which is transformed with the first and second DNA constructs of the invention and (ii) recovering an active binding molecule of the invention from the culture.

Alternatively, the heavy and light chains may be separately recovered and reconstituted into an active binding molecule after in vitro refolding. Reconstitution methods are well-known in the art; Examples of methods are in particular provided in EP 120 674 or in EP 125 023. Therefore a process may also comprise

(i) culturing a first organism which is transformed with a first DNA construct of the invention and recovering said heavy chain or fragment thereof from the culture and

(ii) culturing a second organism which is transformed with a second DNA construct of the invention and recovering said light chain or fragment thereof from the culture and

(iii) reconstituting in vitro an active binding molecule of the invention from the heavy chain or fragment thereof obtained in (i) and the light chain or fragment thereof obtained in (ii).

In a similar manner, there is also provided a process for producing a single chain or single domain binding molecule of the invention which comprises

(i) culturing an organism which is transformed with a DNA construct respectively encoding a single chain or single domain binding molecule of the invention and

(ii) recovering said molecule from the culture.

The binding molecules of the invention significantly inhibit the binding of LINGO-1 to NgR, significantly attenuate the neurite outgrowth inhibitory activity of adult rat spinal cord myelin at sub-nM concentrations and significantly increase oligodendrocyte differentiation in vitro as exemplified below:

Figure legends

Figure 1. Effect of Fabs 4784 and 4785 on AP-LINGO-1 binding to NgR:SH-SY5Y cells

NgR:SH-SY5Y cells in suspension are incubated with either 1 nM AP or AP-LINGO-1 in the absence or presence of 2 µM of the indicated anti-LINGO-1 Fab or anti-hen lysozyme Fab 3207. Bound AP activity on the cells is measured as absorbance at 405 nm after a 30 min incubation with 1-StepTM PNPP. The specific binding of AP-LINGO-1 is calculated as the difference between the total amount of AP-LINGO-1 binding and the amount of binding with AP alone. The mean percentage inhibition of specific binding (n=3, ±STD) is calculated as the percentile difference between the amount of specific binding of AP-LINGO-1 in the presence of Fab 3207 and the presence of an anti-LINGO-1 Fab.

Figure 2. Disinhibition of spinal cord myelin by anti-LINGO-1 IgG4 antibodies 4784 and 4785

A) P7 CGN cells are incubated for 16 hr on wells coated without spinal cord myelin (no SC, white bars) or wells coated with spinal cord myelin in the absence (SC, red bars) or presence of anti-LINGO-1 IgG4 antibodies, a control anti-lysozyme IgG4 antibody 3207 (green bars) or 1 µm of the ROCK inhibitor Y27632 (yellow bar). ROCK is the secondary messenger in the

signaling pathway of most, it not all, myelin-associated neurite outgrowth inhibitors, including those which do not signal through the NgR receptor complex and as such Y27632 treatment is used as a positive control for the attenuation of the neurite outgrowth inhibitory activity of spinal cord myelin (Fig. 1). The experiment is performed in three 96 well plates with an SC and no SC condition per plate to which the effects of the antibodies on that plate are compared and mean neurite length per neuron (μm) is calculated for 500 neurons per well in replicates of 10. The percentage inhibition (white text) is calculated as the percentile difference in mean neurite length/neuron between cells plated on wells coated with and without SC. The percentage disinhibition (black italic text) is calculated as the difference in mean neurite length between cells plated on SC in the presence and absence of anti-LINGO-1 antibody as a percentile of the difference between cells plated on wells coated with and without SC. *$p<0.05$, **$p<0.01$ (one way ANOVA, Holm-Sidak comparison to mean neurite length/neuron for cells plated on spinal cord myelin in the absence of antibody).

B) Fluorescent images of a representative field of view of cells incubated on wells coated without spinal cord myelin (no SC) and on wells coated with spinal cord myelin in the absence (SC) or presence of 1 nM control IgG4 3207 or anti-LINGO-1 IgG4 4784. Cells grown on spinal cord myelin in the presence of 4784 have visibly longer neurites and more neurites per cell than those grown in the absence of antibody or presence of the control antibody 3207.

Figure 3. Disinhibition of spinal cord myelin by anti-LINGO-1 IgG4 antibodies II

A) P7 CGN cells are incubated for 8 hr on wells coated without spinal cord myelin (no SC, white bars) or wells coated with spinal cord myelin in the absence (SC, red bars) or presence of anti-LINGO-1 IgG4 antibodies or a control anti-lysozyme IgG4 antibody 3207. The experiment is performed in three 96 well plates with an SC and no SC condition per plate to which the effects of the antibodies on that plate are compared and mean neurite length per neuron (μm) is calculated for 500 neurons per well in replicates of 10. The percentage inhibition (white text) and disinhibition (black italic text) is calculated as above. **$p<0.01$ (one way ANOVA, Holm-Sidak comparison to mean neurite length/neuron for cells plated on spinal cord myelin in the absence of antibody).

Figure 4. Disinhibition of spinal cord myelin by anti-LINGO-1 IgG4 antibodies III

P7 CGN cells are incubated for 8 hr on wells coated without spinal cord myelin (no SC) or wells coated with spinal cord myelin in the absence (SC) or presence of the indicated concentrations of anti-LINGO-1 IgG4 antibodies 4784 or 4785, a control anti-lysozyme IgG4 antibody 3207 or 1 μM Y27632 (ROCK). The experiment is performed in three 96 well plates with an SC and no SC condition per plate to which the effects of the antibodies on that plate are compared and mean neurite length per neuron (μm) is calculated for 500 neurons per well in replicates of 10. The percentage inhibition (white text) and disinhibition (black italic text) is calculated as above. *p<0.05, **p<0.01 (one way ANOVA, Holm-Sidak comparison to mean neurite length/neuron for cells plated on spinal cord myelin in the absence of antibody).

Figure 5. Anti-LINGO-1 antibodies significantly increase the differentiation of immature oligodendrocytes

A) Freshly isolated OPCs are treated with 100 nM 4784, 4785 or control IgG4 3207 for 3 days in DMEM/CNTF/T3 medium followed by staining with the anti-O4 antibody to visualise immature and mature oligodendrocytes (larger, more diffuse labeling) and the nucleic acid dye DAPI (4',6-diamidin-2'-phenyl-indol-dihydrochloride) to visualise cell nuclei (smaller circular dots). Oligodendrocytes bearing highly arborised and extended processes and myelin sheet-like structures are considered to have a mature morphology and are indicated with white arrows. Anti-LINGO-1 antibody treatment results in an increase in the proportion of O4-postive cells with a mature morphology whereas treatment with control IgG4 3207 has no effect.

B) The proportion of total (left graph) and mature (right graph) oligodendrocytes is quantified in three independent experiments (1,2,3). The left bar graph depicts the percentage of DAPI-stained nuclei associated with O4-staining and the right bar graph depicts the percentage of O4-positive cells with a mature morphology (mean of triplicates + STD). In each bar graph, the leftmost bar is with no treatment, the second to left bar Control with Control IgG, the next represents treatment with 4784 and the rightmost treatment with 4785. Anti-LINGO-1 antibodies have no effect on the proportion of cells that are oligodendrocytes but significantly increase the proportion of oligodendrocytes with a mature morphology. * p<0.05, ** p<0.01, one-way ANOVA with a Holm-Sidak comparison to the proportion of mature oligodendrocytes in the presence of the control IgG4 3207.

Figure 6. Anti-LINGO-1 antibodies downregulate cell surface LINGO-1

A) Untransfected CHO-K1 or CHO-K1-hLINGO-1 cells are incubated at 37°C for 24 hrs with 100 nM 4784, 4785 and 3207 and LINGO-1 detected at the cell surface by a further incubation at room temperature for 30 min with the anti-V5 antibody. The cells are fixed with 4% PFA, blocked with BSA and bound anti-V5 antibody detected using an anti-mouse-IgG (Fc specific)-POD conjugate that is subsequently developed using a 1-Step™ Turbo TMB ELISA kit. The absorbance at 450 nm is taken as a measure of the amount of LINGO-1 at the cell surface (mean of triplicates ± STD). A very low level of anti-V5 antibody binding is observed to untransfected CHO-K1 cells. Incubation of CHO-K1-hLINGO-1 cells with anti-LINGO-1 antibodies but not the control IgG4 3207 result in a significant reduction in the amount of LINGO-1 at the cell surface ** $p<0.01$, one-way ANOVA with a Holm-Sidak comparison to the absorbance following incubation with the control IgG4 3207.

B) Cell surface proteins on untransfected CHO-K1 or CHO-K1-hLINGO-1 cells are biotinylated at 4°C and the cells are incubated at 37°C for the indicated times with or without 100 nM 4784, 4785 and 3207. At the end of the incubation period, LINGO-1 is precipitated from the cell lysate using the anti-V5 antibody coupled to agarose beads and biotinylated (cell surface) LINGO-1 detected by Western blot analysis using an anti-biotin antibody. No signal is detected for biotinylated LINGO-1 in untransfected CHO-K1 cells. Incubation of CHO-K1-hLINGO-1 cells with anti-LINGO-1 antibodies increases the rate of degradation of cell surface LINGO-1.

Figure 7. Characterization of anti-LINGO-1 Fabs by ELISA

Values for ELISA analyses are given as mean values of relative fluorescence units (RFU). The binding affinities of these clones are characterized by FACS saturation assays.

The present invention also provides the use of the binding molecules of the invention in the promotion of axonal regeneration/plasticity of a mammalian nervous system, in particular the human nervous system.

The invention also provides a method of promoting axonal regeneration/plasticity of a mammalian nervous system, in particular human nervous system which comprises

administering an effective amount of the binding molecules of the invention to a patient in need of such treatment.

The invention also provides a pharmaceutical composition for promoting axonal regeneration/plasticity of a mammalian nervous system, in particular human nervous system which comprises the binding molecules of the invention and a pharmaceutically acceptable carrier or diluent.

In particular, the binding molecules of the invention are useful for promoting axonal regeneration and plasticity after CNS injury (the term injury, in the present application, refers especially to injury caused by mechanical or chemical effects or due to diseases or disorders that e.g. lead to degeneration of neurons, especially their structure or form, e.g. in neurological diseases such as Alzheimer's or Parkinson's Disease or other disorders or dieseases mentioned below). Thus the molecules of the invention have a wide utility in particular for human subjects. For example the binding molecule of the invention are useful in the treatment of various diseases of the peripheral (PNS) and central (CNS) nervous system, i.e. more particularly in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis (ALS), Lewy like pathologies or other dementia in general, diseases following cranial, cerebral or spinal trauma and stroke. Furthermore, given that LINGO-1 is a negative regulator of myelination, the binding molecules of the invention are useful for promoting remyelination in concert with promoting axonal regeneration/plasticity in demyelinating diseases that include, but are not limited to, multiple sclerosis, monophasic demyelination, encephalomyelitis, multifocal leukoencephalopathy, panencephalitis, Marchiafava-Bignami disease, pontine myelmolysis, adrenoleukodystrophy, Pelizaeus-Merzbacher disease, Spongy degeneration, Alexander's disease, Canavan's disease, metachromatic leukodystrophy and Krabbe's disease. In one example, cells which express the binding molecules of the invention may be transplanted to a site spinal cord injury to facilitate axonal growth throughout the injured site. Such transplanted cells would provide a means for restoring spinal cord function following injury or trauma. Such cells could include olfactory ensheathing cells and stem cells of different lineages of fetal nerve or tissue grafts.

In addition, the binding molecules of the invention are useful for the treatment of degenerative ocular disorders which may directly or indirectly involve the degeneration of retinal or corneal cells including ischemic retinopathies in general, anterior ischemic optic neuropathy, all forms of optic neuritis, age-related macular degeneration, diabetic retinopathy, cystoid macular edema (CME), retinitis pigmentosa, Stargardt's disease, Best's vitelliform retinal degeneration, Leber's congenital amaurosis and other hereditary retinal degenerations, pathologic myopia, retinopathy of prematurity, and Leber's hereditary optic neuropathy, the after effects of corneal transplantation or of refractive corneal surgery, and herpes keratitis.

Furthermore, the binding molecules of the invention are useful for the treatment of psychiatric conditions, particularly schizophrenia and depression.

For these indications, the appropriate dosage will, of course, vary depending upon, for example, the particular molecule of the invention to be employed, the mode of administration and the nature and severity of the condition being treated. In general, the dosage preferably will be in the range of 1 μg/kg/day to 1 mg/kg/day. The binding molecules of the invention are conveniently administered by pumps or injected as therapeutics at the lesioned site or near it, e.g. they can be administered directly into the CNS intracranially or into the spine intrathecally to the lesioned site. However, systemic administration is not excluded here. The binding molecules of the invention can be provided alone, or in combination, or in sequential combination with other agents. For example, the binding molecules of the invention can be administered in combination with anti-Nogo-A antibodies or anti-inflammatory agents such as but not limited to corticosteroids following stroke or spinal cord injury as a means for blocking further neuronal damage and inhibition of axonal regeneration, neurotrophic factors such as NGF, BDNF or other drugs for neurodegenerative diseases such as Exelon™ or Levodopa. Other suitable combination partners for the treatment of stroke are Alteplase and Desmoteplase (DSPA, e.g. disclosed in WO90/09438). In one embodiment, the present invention provides a combination comprising a binding molecule of the invention and Desmoteplase, in particular for the treatment of stroke as well as pharmaceutical compositions comprising said combination. As used herein, two agents are said to be administered in combination when the two agents are administered

simultaneously or are administered independently in a fashion such that the agents will act at the same time.

The structure of the active ingredients identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications) or other databases provided by IMS Health. The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active ingredients and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both *in vitro* and *in vivo*.

Pharmaceutical compositions of the invention may be manufactured in conventional manner. E.g. a composition according to the invention comprising the molecules of the invention is preferably provided in lyophilized form. For immediate administration it is dissolved in a suitable aqueous carrier, for example sterile water for injection or sterile buffered physiological saline.

To aid in making up suitable compositions, the binding molecules of the invention and optionally a second drug enhancing the effect of the binding molecules of the invention, may be packaged separately within the same container, with instructions for mixing or concomitant administration. Optional second drug candidates are provided above.

The synergistic effect of a combination of the binding molecules of the invention and growth factors such as NGF may be demonstrated in vivo by the spinal cord injury models.

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

The monoclonal antibodies of attention in the Examples are binding molecules according to the present invention containing for antibody 4784 the variable part of the light chain (SEQ ID NO: 4) and the variable part of the heavy chain (SEQ ID NO: 5) and comprising for 4785

the variable part of the light chain (SEQ ID NO: 6) and the variable part of the heavy chain (SEQ ID NO: 7).

The following abbreviations are used:

AP	human placental alkaline phosphatase
CDR	complementarity determining region
cDNA	complementary DNA
ELISA	enzyme linked immuno-sorbant assay
FACS	fluorescence activated cell sorting
FBS	foetal bovine serum
HCMV	human cytomegalovirus promoter
IgG	immunoglobulin isotype G
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PFA	paraformaldehyde
PNPP	para-nitrophenyl phosphate

Example 1: Generation of CHO-K1 cells expressing full length rat, cynomolgus monkey or human LINGO-1 and human LINGO-2

A human cDNA library is generated by RT-PCR of universal human reference RNA (Stratagene) using random and oligo dT primers. A cynomolgus monkey brain cDNA library is generated by RT-PCR of polyA RNA isolated from frozen cynomolgus monkey brain using random and oligo dT primers. A Marathon-ready rat brain cDNA library is obtained from Clontech. cDNA encoding the mature sequence (residues 34-614) of human LINGO-1 (SEQ ID NO: 27), cynomolgus monkey LINGO-1 (SEQ ID NO: 28) and rat LINGO-1 (SEQ ID NO: 29) flanked by 5′-XbaI and 3′-XhoI sites is PCR amplified from the respective library using the forward primer DM14, 5′-CTACGTCTAGAACGGGCTGCCCGCCCCGCT-3′ (SEQ ID NO: 30), and reverse primer DM15, 5′-GGTTTCTCGAGTCATATCATCTTCATGTTGAACTTGCGG-3′ (SEQ ID NO: 31). The PCR product is cleaved with XbaI and XhoI and inserted into the respective sites of the vector pSecTag2-V5 (SEQ ID NO: 32) to generate hLINGO-1-pSecTag2-V5, cmLINGO-1-pSecTag2-V5 and rLINGO-1-pSecTag2-V5, respectively. The predicted protein product is

the mature sequence of LINGO-1 fused at the N-terminus to a 14 amino acid residue V5 epitope tag via a 2 amino acid residue linker. cDNA encoding the mature sequence (residues 26-606) of human LINGO-2 (SEQ ID NO: 33) flanked by 5′-XbaI and 3′-XhoI sites is PCR amplified from a Marathon-ready human brain cDNA library (Clontech) using the forward primer DM16, 5′-CTACGTCTAGAATTGGCTGCCCCGCTCGCT-3′ (SEQ ID NO: 34), and reverse primer DM17, 5′-GGTTTCTCGAGTCAAATCATTTTCATGTTGAACCTCCTG-3′ (SEQ ID NO: 35). The PCR product is cleaved with XbaI and XhoI and inserted into the respective sites of the vector pSecTag2-V5 to generate hLINGO-2-pSecTag2-V5. The predicted protein product is the mature sequence of LINGO-2 fused at the N-terminus to a 14 amino acid residue V5 epitope tag via a 2 amino acid residue linker. CHO-K1 cells stably expressing human LINGO-1 (CHO-K1-hLINGO-1), cynomolgous LINGO-1 (CHO-K1-cmLINGO-1), rat LINGO-1 (CHO-K1-rLINGO-1) and human LINGO-2 (CHO-K1-hLINGO-2) are generated by transfection of cells with hLINGO-1-pSecTag2-V5, cmLINGO-1-pSecTag2-V5, rLINGO-1-pSecTag2-V5 and hLINGO-2-pSecTag2-V5, respectively, using lipofectamine-2000 (Invitrogen) according to the manufacturer's instructions. Stably expressing transfectants are selected with 1 mg/ml zeocin (Invivogen) and single clones isolated either by serial dilution into 96-well plates or by using clonal rings. Expression of the constructs on the cell surface is confirmed by immunofluorescent analysis using an anti-V5 antibody (InvitroGen).

Example 2: Generation and expression of human LINGO-1-Fc and human LINGO-1ΔLRR-Fc

A MGC mRNA coding for human LINGO-1 (clone MGC:17422 IMAGE:4214343) is used as template for PCR amplification. The extracellular domain (ECD) preceded by the natural signal sequence (aa1-550) of human LINGO-1 is amplified by PCR with the Pwo1 polymerase (Roche Diagnostics) and with primers which added a HindIII restriction site and a Kozak consensus sequence at the 5' end of the target sequence and an XhoI restriction site immediately after the last codon of the target sequence at the 3' end. The PCR product is digested with HindIII and XhoI, gel purified and inserted into plasmid pRS5a-IgG (SEQ ID NO: 36) previously digested with the same enzymes. The accuracy of the inserted

sequence, complete Fc and flanking regions in the resulting expression clone (natleader-hsLINGO-1-Fc/pRS5a, SEQ ID NO: 37) is confirmed by DNA sequencing.

The same MGC clone serves as template for the construction by gene SOEing of the expression plasmid for human LINGO-1 lacking the LRR domain (aa34-65 + aa354-550). The N-terminal region of human ECD LINGO-1 (aa34-65) is amplified by PCR with primers extending the 5' end with a partial sequence coding for an heterologous secretion signal fused to mature LINGO-1 and adding, at the 3' end, a sequence coding for the first seven amino acids of the C-terminal fragment. The C-terminal region of human ECD LINGO-1 (aa354-550) is amplified by PCR with primers extending the 5' end with a sequence coding for the last seven amino acids of the N-terminal fragment and adding, at the 3' end, an XhoI site immediately after the last codon of the target sequence. The two PCR products are gel purified, mixed and serves as template for a second PCR amplification using at the 5' end a primer which adds a HindIII restriction site, a Kozak consensus sequence and completes the herologous secretion signal sequence and, at the 3' end, the external primer previously used to amplify the C-terminal fragment. The PCR product is digested with HindIII and XhoI, gel purified and inserted into plasmid pRS5a-IgG previously digested with the same enzymes. The accuracy of the inserted sequence, complete Fc and flanking regions in the resulting expression clone (Igleader-hsLINGO-1-ΔLRR-Fc/pRS5a, SEQ ID NO: 38) is confirmed by DNA sequencing.

As an initial expression evaluation both constructs are tested in small scale experiments. HEK.EBNA cells (Invitrogen, previous cat.no. R620-07) are cultivated in attached mode on tissue culture flasks in Dulbecco's Modified Eagle Medium (DMEM) buffered with 25 mM Hepes (Gibco/Life Technologies cat.no. 42430-025) and additionally enriched with 10% fetal calf serum; the cultures are maintained at 37°C and 5% CO_2 in humidified atmosphere. For small scale transfection experiments, $4x10^5$ cells are seeded one day prior to transfection into poly-D-lysine-coated 6-wells (plates). Transfections are performed using 3 µg of plasmid DNA and 6 µl of Lipofectamine^{2000} reagent (Invitrogen cat.no. 11668-019) per well, essentially as described by the vendor. Three days post-transfection the cell supernatants are harvested and the cell-free supernatant is subjected to protein analysis, i.e. to immuno-affinity HPLC analysis on Protein G columns. Titers ranging between 8 mg/l for construct natleader-hsLINGO-1-Fc/pRS5a and 40 mg/l for construct Igleader-hsLINGO-1-ΔLRR-Fc/pRS5a are determined. Subsequently, for both plasmids large-scale plasmid preps are

prepared to enable transient transfections on the multi-litre scale in HEK.EBNA suspension cultures.

For production of natleader-hsLINGO-1-Fc on enlarged scale, 2.9 L of HEK.EBNA cell culture at a density of $1.4x10^6$ cells/ml is mixed with 1.1 L DNA:PEI solution (1 µg DNA:2 µg PEI per ml). Following incubation of cells for 4 hrs, the culture is fed with 4 L of ExCell VPRO medium (SAFC, previously JRH, Lenexa, KS). The cell culture supernatant is harvested after 6 days of cultivation and concentrated by diafiltration down to 1-L using a disposable Hemoflow F10HPS filter with a 10 kDa cut-off (Fresenius Medical Care, Germany).

The second relevant protein production run to generate Igleader-hsLINGO-1-ΔLRR-Fc protein is done in a similar fashion. Details on large-scale transfection, DNA:PEI ratio, cell densities, feeding and harvest are exactly the same as described above.

a) natleader-hsLINGO-1-Fc

1 L concentrate (from 8 L culture supernatant) is chromatographed on 20 ml Protein A Sepharose. After base-line washing with 100 mM NaPi, pH 7.3, bound material is eluted with 50 mM citrate, 140 mM NaCl, pH 2.7, neutralized and sterile filtered. The eluted fraction is further concentrated and gel filtered on Superdex 75 in PBS yielding 8.2 mg product at a concentration of 1.2 mg/ml.

b) Igleader-hsLINGO-1-ΔLRR-Fc

1 L concentrate (from 8 L culture supernatant) is chromatographed on 20 ml Protein A Sepharose. After base-line washing with 100 mM NaPi, pH 7.3, bound material is eluted with 50 mM citrate, 140 mM NaCl, pH 2.7, neutralized and sterile filtered yielding 52.5 mg product at a concentration of 1.5 mg/ml.

The purified proteins are extensively characterized by N-terminal sequencing and by MALDI peptide mass analysis after reduction/alkylation and trypsin digestion.

Example 3: AP-LINGO-1 binding assay

Blocking the binding of LINGO-1 to NgR is expected to prevent the signaling of three myelin-associated inhibitors of neurite outgrowth, namely Nogo-66, MAG and OMgp, and hence attenuate the neurite outgrowth inhibitory activity of CNS myelin thus leading to increased axonal regeneration/plasticity and improved functional recovery following acute CNS injury.

To demonstrate that an anti-LINGO-1 antibody blocks the binding of LINGO-1 to NgR, an assay can be used which measures the binding of human placental alkaline phosphatase (AP)-tagged rat LINGO-1 ectodomain (AP-LINGO-1) to SH-SY5Y cells stably expressing NgR (NgR-SH-SY5Y, Walmsley et. al. (2004) J Cell Sci 117, 4591-4602).
cDNA encoding the majority of the rat LINGO-1 ectodomain (residues 34-532) flanked by 5′-Xho I and 3′-Xba I sites is PCR amplified from rLINGO-1-pSecTag2-V5 using the forward primer DM22, 5′-GGTTATCTCGAGACCGGCTGCCCGCCCC-3′ (SEQ ID NO: 24), and reverse primer DM23, 5′-GGCCCTTCTAGATCACTCGCCTGGCTGGTTGGAGATG-3′ (SEQ ID NO: 25). The PCR product is cleaved with XhoI and XbaI and inserted into the respective sites of the vector APtag-5-NHIS (SEQ ID NO: 26) to generate APtag-5-NHIS-solrLINGO-1. The predicted protein product is the majority of the rat LINGO-1 ectodomain fused at the N-terminus to residues 23-511 of human placental alkaline phosphatase via a 3 amino acid residue linker. HEK293T cells are transfected with APtag-5-NHIS-solrLINGO-1 using lipofectamine^{2000} according to the manufacturer's instructions. The transfection medium is removed 4 hrs after transfection and replaced with OptiMEM I without phenol red (Invitrogen). Medium is harvested after 24 hrs, replaced and harvested again after another 24 hrs. The medium is clarified by centrifugation at 13000xg for 5 min and the supernatant concentrated around 15-fold using a Centriprep filter device (Millipore) according to the manufacturer's instructions. AP activity of the concentrated supernatant is measured using 1-Step™ PNPP (Pierce) as change in absorbance at 405 nm over time and transformed to a concentration using the following equation (applies for a 96 well plate format with 200 µl PNPP/well):

$$\text{Concentration of AP-fusion (nM)} = \frac{\text{Change in absorbance (mAU/min)}}{7.945 \times \text{volume of sample added to PNPP(µl)}}$$

Concentrated supernatant is subjected to SDS-PAGE gel electrophoresis and Western blotted as described (Walmsley et. al. (2004) J Cell Sci 117, 4591-4602). AP-LINGO-1 is detected with 0.1% (v/v) anti-penta-histidine antibody (Qiagen) followed by 0.02% (v/v) peroxidase-conjugated anti-mouse IgG antibody (Sigma) using the ECL™ system (GE Healthcare). AP-LINGO-1 is visualised as a band of approximately 110 kDa, similar to its predicted molecular weight of 112kDa. No N-terminal degradation products are observed.

NgR:SH-SY5Y cells at 50% confluency are harvested with enzyme-free dissociation buffer (Invitrogen) to preserve cell surface proteins such as NgR. 1 nM AP, 1 nM AP-LINGO-1 or 1 nM AP-LINGO-1 in the presence of 2 µM anti-LINGO-1 Fab or a control Fab 3207 against lysozyme from hen egg white is pre-incubated for 30 min in OptiMEM (Invitrogen) and subsequently incubated with constant agitation for 1.5 hr with NgR:SH-SY5Y cells in suspension. Cells are washed 6 times in HBH (20 mM HEPES pH 7.4/1% bovine serum albumin in Hanks balanced saline) and fixed in 4% paraformaldehyde (PFA)/5% sucrose in PBS for 15 min. Following inactivation of endogenous AP activity by incubation at 65°C for 1 hr in 20 mM HEPES pH 7.4 in Hanks balanced saline, cell-bound AP activity is quantified as absorbance at 405 nm after a 30 min incubation with 1-Step™ PNPP (Pierce) according to the manufacturer's instructions.

The Fabs are used at a concentration of 2 µM in order to saturate AP-LINGO-1 with bound Fab and thus minimise the influence of their affinities on their ability to inhibit binding. The reason for this is to exclude the possibility of prematurely discarding Fabs from further studies which fail to inhibit binding due to their low affinity rather than the position of their binding site as the affinity of such Fabs could be increased at later stages by affinity maturation and IgG4 conversion. 1 nM AP-LINGO-1 is pre-incubated with either the control Fab 3207 or anti-LINGO-1 Fabs 4784 and 4785 and then allowed to bind in the presence of the Fab to NgR:SH-SY5Y cells in suspension (Fig. 1). The percentage inhibition in specific AP-LINGO-1 binding in the presence of the anti-LINGO-1 Fabs is normalized to that for Fab 3207. 4784 and 4785 give a significant inhibition ($p<0.01$, one way ANOVA, Holm-Sidak comparison to specific binding of AP-LINGO-1 in presence of control Fab 3207) of AP-LINGO-1 binding to the cells.

Blocking the binding of LINGO-1 to NgR is predicted to prevent the signaling of the myelin-associated inhibitors Nogo-66, MAG and OMgp leading to a reduction in the neurite outgrowth inhibitory activity of CNS myelin. In that regard, 4784 and 4785 Fabs are converted to the final IgG4 format (see Example 8) and assessed for their ability to attenuate the inhibition of neurite outgrowth from postnatal day 7 rat cerebellar granule neurons grown on adult rat spinal cord myelin.

Example 4: Neurite outgrowth inhibition assay

The most relevant in vitro assay to predict the effect of anti-LINGO-1 antibodies on axonal regeneration/plasticity in vivo is their ability to attenuate the neurite outgrowth inhibitory activity of CNS myelin. In this assay, postnatal day 7 rat cerebellar granule neurons (CGN) are grown in wells coated with whole spinal cord myelin extracted from adult rats and neurite outgrowth quantified by an automated ArrayScan® HCS Reader (Cellomics).

The disinhibitory activity of anti-LINGO-1 IgG4 antibodies 4784 and 4785 is assessed in the said neurite outgrowth assay (Fig 2).

Fresh rat spinal cord tissue from adult rats is homogenized in 3 volumes (w/v) extraction buffer (60 mM Chaps, 20 mM Tris pH 8.0, 1 mM EDTA, protease inhibitor cocktail), incubated for 30 min at 4°C and clarified by centrifugation at 170000xg for 30 min at 4°C. Each well in a 96 well plate is coated with 5 µl nitrocellulose in MeOH (5 cm^2 nitrocellulose in 12 ml MeOH), air dried and coated with 100 µl 5 µg/ml poly-D-lysine by incubation for 4 hr at 37°C. Following three washes in water, the plates are air dried for 1 hr and then coated with 60 µg/cm^2 spinal cord extract by incubation overnight at 37°C. CGN cells are freshly purified from trypsin dissociates of postnatal day 7 rat cerebellar tissue as described previously (Schweigreiter et al., 2004). Western blot analysis to detect LINGO-1 is performed on lysates from CHO-K1 cells expressing V5-tagged rat LINGO-1 or P7 CGN cells using 2µg/ml (or 13.3 nM) anti-LINGO-1 polyclonal antibody (Upstate) followed by 0.02 % (v/v) peroxidase-conjugated anti-rabbit IgG antibody (Sigma). CGN cells (35000 cells /well) are incubated for 30 min at 37°C on wells coated without or with spinal cord myelin prior to the addition of either 0-100 nM anti-LINGO-1 IgG4 antibody or the control 3207 IgG4 antibody. Following an 8-16 hr incubation at 37°C, cells are fixed with 4% PFA and stained with Hoechst 3342 (Invitrogen) for visualisation of the nucleus and anti-β-tubulin III antibody (R&D Systems) followed by an Alexa Fluor 546-conjugated anti-mouse IgG antibody (Invitrogen) to specifically visualize neurons. Parameters of neurite outgrowth are determined using an ArrayScan® HCS Reader (Cellomics). ArrayScan® II automatically locates, focuses and exposes fields of cells within a 96-well microtiter plate. ArrayScan® consists of a high-resolution optical system, a multiple bandpass emission filter with matched single band excitation filter (XF100), a CCD camera with frame grabber, and proprietary applications software. In this assay, the Extended Neurite Outgrowth Bioapplication is used.

An excitation filter wheel and multiple bandpass emission filters are used to enable multichannel imaging of fluorescence from two fluorophores in the same cells. Bandpass images of Hoechst 33342-labelled nuclei are acquired to identify discrete cells, and bandpass images of Alexa Fluor 488 are then acquired to indentify the extent of cells labeled with anti-tubulin antibody (using a secondary conjugated to Alexa Fluor 488). Inappropriate bodies within cells are automatically excluded from the analysis, so that only overlapping Hoechst and beta-tubulin cell bodies are analyzed. Dual emission images are acquired for 5 discrete 350 μm^2 fields in each well of the plate. Using a 10-x objective, this results in 400-500 cells per well analyzed. The Extended Neurite Outgrowth Bioapplication then reports several quantitative measures of neuronal morphology for single cells, including neurite length number of neurites per cell, cell body area, and branch and cross points. The mean neurite length per neuron (µm) is calculated for 500 neurons per well in replicates of 10.
In the above neurite outgrowth assay, the anti-LINGO-1 IgG4 antibodies 4784 and 4785 are disinhibitory at 1 and 10 nM, whereas the control IgG4 against lysozyme gives no disinhibition at both concentrations (Fig. 2). The mean length of neurites per neuron on spinal cord myelin in the presence of 4784 and 4785 at both concentrations is statistically higher than that in the absence of antibody. The greater level of disinhibition achieved with the ROCK inhibitor Y27632 compared to the anti-LINGO-1 antibodies 4784 and 4785 is expected as this compound inhibits the signaling pathways of additional myelin-associated neurite outgrowth inhibitors other than those that signal through the NgR receptor complex.

To confirm the above results, the neurite outgrowth assay is repeated (Fig. 3). Again, the anti-LINGO-1 antibodies 4784 and 4785 are disinhibitory at 1 nM and 10 nM, whereas the control IgG4 against lysozyme gives no disinhibition at both concentrations. The mean length of neurites per neuron on spinal cord myelin in the presence of 4784 and 4785 at both concentrations is statistically higher than that in the absence of antibody.

To further establish the potency of the anti-LINGO-1 antibodies 4784 and 4785, the effect on neurite outgrowth inhibition of sub-nM concentrations of the antibody is assessed (Fig. 4). 4784 and 4785 give a significant disinhibition (38-51% and 51-57%, respectively) of spinal cord myelin at concentrations as low as 0.1 nM, whereas the control anti-lysozyme antibody

has no effect. Again, the ROCK inhibitor Y27632 gives a higher degree of disinhibition (65-74%) than the anti-LINGO-1 IgG4 antibodies as expected.

Example 5: Primary oligodendrocyte differentiation assay

Blockade of LINGO-1 function by genetic means or by treatment with a receptor-body antagonist has been reported to increase the proportion of mature oligodendrocytes arising from purified OPC cultures (Mi et al. (2005) Nat Neurosci 8, 745-751). To assess the ability of anti-LINGO-1 antibodies to block LINGO-1 function in OPC cultures and promote oligodendrocyte maturation, freshly isolated rat OPCs are incubated with 4784, 4785 or control IgG4 3207 for 3 days in DMEM/CNTF/T3 medium followed by staining with the anti-O4 antibody to label both immature and mature oligodendrocytes (Fig 5). The degree of oligodendrocyte maturation is measured as the proportion of O4-positive cells exhibiting a mature morphology.

Enriched populations of OPCs are isolated from OFA P3 rats. Briefly, the brain is dissected and the telencephalons are placed in ice-cold Hank's buffered saline solution (HBSS, Invitrogen) containing 0.15% $MgSO_4$. The tissue is incubated with 1:1 HBBS/trypsin-EDTA (Invitrogen) and 100 μg/ml DNAse I (Roche) for 10 min at 37°C and the trypsin inactivated by addition of FCS (Invitrogen) to a final concentration of 10%. The tissue suspension is centrifuged at 890 rpm for 10 min and the pellet resuspended in Basal Medium Eagle (BME, Invitrogen) with 10% horse serum (Invitrogen). The suspension is filtered through a 40 μm cell strainer (BD Falcon) and the cells plated on poly-D-lysine pre-coated 80 cm^2 tissue culture flasks (BD Falcon) at 1 brain per flask. Cells are cultivated at 37°C for 11 days in BME/10% horse serum. Microglial cells are killed by adding 5 mM L-leucine-methyl esther and the flasks are agitated by shaking at 140 rpm for 2 hrs. OPCs are harvested by shaking the flasks overnight at 200 rpm at 37°C and any astrocytes remaining in the supernatant are further separated from the OPCs by pre-attachment for 2 hrs at 37°C on 10 cm bacterial culture dishes. Non-adherent cells are collected, centrifuged for 10 minutes at 890 rpm and plated at approximately 3 x 10^4 cells/well in poly-D-lysine-coated 8-well chamber slides (BD Falcon). Cultures are maintained for 3 days in either in DMEM/T3/CNTF medium consisting of DMEM (Invitrogen) containing 10 ng/ml Ciliary Neurotrophic Factor (R&D Systems) and 15 nM Triiodothyronine (Sigma) or in SATO medium consisting of DMEM (Invitrogen)

containing 10 μg/ml transferrin (Sigma), 10 μg/ml insulin (Sigma), 100 μM putrescine (Sigma), 200 nM progesterone (Sigma), 520 nM thyroxine (Sigma), 500 pM Triiodothyronine (Sigma), 220 nM sodium selenite (Sigma), 25 μg/ml gentamycin (Sigma) and 1% HS (Invitrogen). To assess the purity of the cultures with respect to the oligodendrocyte lineage, the percentage of cells that are stained with the anti-O4 antibody is quantified after 7 days of culture in SATO medium. Typically, 80-95% of the cells are stained with the anti-O4 antibody demonstrating that the majority of the cells in the culture are of the oligodendrocyte lineage.

To assess oligodendrocyte maturation based on oligodendrocyte morphology, freshly isolated OPC cultures are incubated in DMEM/T3/CNTF medium for 3 days in the absence or presence of 100 nM 4784, 4785 or control IgG4 3207 followed by staining with the anti-O4 antibody to label both immature and mature oligodendrocytes and DAPI to label cell nuclei. O4-positive cells with clearly defined short processes are considered to represent immature oligodendrocytes whereas O4-positive cells bearing extended and highly arborised processes with myelin sheet-like structures are considered to represent mature oligodendrocytes. The proportion of O4-positive cells with a mature morphology is quantified for around 300-1300 cells in triplicate per treatment and significance determined using one-way ANOVA with a Holm-Sidak comparison to the proportion of mature oligodendrocytes in the presence of the control IgG4 3207. To assess the effect of the antibody treatment on the proportion of total (immature and mature) oligodendrocytes in the culture, the proportion of DAPI nuclei associated with O4-staining is quantified.

In three independent experiments, treatment with the anti-LINGO-1 antibodies 4784 and 4785 significantly increases the proportion of oligodendrocytes with a mature morphology as represented by cells bearing highly arborised processes that extend over a wide area and myelin sheet-like structures (Fig 5). Treatment with the control IgG4 antibody 3207 has no effect on the proportion of mature oligodendrocytes in the culture. The proportion of DAPI-stained nuclei associated with O4-staining is similar for all treatments, demonstrating that anti-LINGO-1 antibodies have no effect on the proportion of cells corresponding to both immature and mature oligodendrocytes.

As anti-LINGO-1 antibody treatment has no effect on the proportion of total oligodendrocytes, the increase in the proportion of mature oligodendrocytes most likely arises due to an increase in the rate of differentiation of immature oligodendrocytes to

mature oligodendrocytes rather than an increase in the rate of differentiation of OPCs to immature oligodendrocytes.

Example 6: Anti-LINGO-1 antibody-mediated downregulation of cell surface LINGO-1

The binding of multi-valent antibodies to cell surface targets can lead to the internalisation of the antibody:target complex and subsequent degradation of the target within the endocytic pathway (Weinmann et al. (2006) Mol Cell Neurosci 32, 161-173).

To determine the effect of anti-LINGO-1 antibodies on the amount of cell surface LINGO-1, untransfected CHO-K1 or CHO-K1-hLINGO-1 cells (see Example 1) are incubated at 37°C for 24 hrs with 100 nM 4784, 4785 or 3207 and cell surface LINGO-1 is subsequently detected with an anti-V5 antibody followed by an anti-mouse IgG (Fc specific)-POD conjugate developed with a 1-Step™ Turbo TMB-ELISA kit (Pierce) (Fig 6A).

The amount of cell surface LINGO-1 in CHO-K1-hLINGO-1 cells is significantly reduced following a 24 hr incubation with anti-LINGO-1 antibodies 4784 and 4785, whereas incubation with the control IgG4 3207 ha s no effect. In addition, incubation with 4785 reduces cell surface LINGO-1 to a greater extent than 4784.

To assess the effect of anti-LINGO-1 antibodies on the degradation of cell surface LINGO-1, cell surface proteins on untransfected CHO-K1 or CHO-K1-hLINGO-1 cells are biotinylated at 4°C as described (Walmsley et al. (2004) J Cell Sci 117, 4591-4602) and the cells incubated at 37°C for various times over a 180 min period with or without 100 nM 4784, 4785 or 3207 (Fig 6B). At the end of the incubation period, LINGO-1 is immunoprecipitated from the cell lysate using anti-V5 antibody coupled to agarose beads and biotinylated LINGO-1 detected in the precipitate by Western blot analysis using an anti-biotin antibody (Sigma).

The intensity of the band corresponding to biotinylated (and hence cell surface) LINGO-1 diminishes more rapidly in CHO-K1-hLINGO-1 cells incubated with the anti-LINGO-1 antibodies 4784 and 4785 than in cells incubated without antibody or with the control IgG4 3207. In addition, incubation with 4785 increases the rate of degradation of cell surface LINGO-1 to a greater extent than 4784.

These results cumulatively show that anti-LINGO-1 antibodies 4784 and 4785 significantly downregulate LINGO-1 at the cell surface most likely by augmenting the internalisation and

degradation of the protein. This property is expected to contribute to the efficacy of these antibodies in blocking LINGO-1 function.

Example 7: Enzyme Linked Immunosorbent Assay (ELISA) and FACS Techniques

Human recombinant LINGO-1-Fc fusion protein is immobilized onto Maxisorp plates 96 or 384 well for 1h at RT indirectly by capturing of the Fc part via a directly immobilized goat anti-human IgG Fc antibody (100µl or 20µl coated at 10 µg/ml in PBS).
After coating of 20µl of the antigen at 5µg/ml in PBS, the wells are blocked with PBS / 0.05% Tween (PBS-T) / 5% milk powder for 1 h at RT. After washing the wells with PBS-T BEL-extracts, purified Fabs or control IgGs are diluted in PBS, added to the wells and incubated for 1 h at RT. To detect the primary antibodies, the following secondary antibodies are applied: alkaline phospatase (AP)-conjugated AffiniPure goat $F(ab')_2$ fragment anti-human IgG or anti-mouse IgG (Jackson ImmunoResearch). For the detection of AP-conjugates fluorogenic substrates like AttoPhos (Roche) are used according to the manufacturers' instructions. Between all incubation steps, the wells of the microtiter plate are washed with PBS-T five times and five times after the final incubation with secondary antibody. Fluorescence is measured in a TECAN Spectrafluor plate reader.

FACS analysis of antibody binding to LINGO-1 expressed on the cell surface of transfected CHO-K1 cells

All stainings are performed in round bottom 96-well microtiter plates (NUNC™, Wiesbaden, Germany) with $2x10^5$ cells per well. Cells of the respective cell line are resuspended in PBS / 3% FCS / 0.02% NaN_3 (FACS buffer) and mixed with a) antibody from periplasmic extracts or BEL lysates or b) purified Fab fragments or c) purified IgG diluted in FACS buffer and incubated at 4°C for 30-60 min. Cells are then washed once with 150µl FACS buffer / well and taken up in 100 µl phycoerythrin-labeled secondary antibody (R-PE conjugated goat anti-human IgG (H+L) (Jackson ImmunoResearch) which has been diluted 1:200 in FACS buffer. After incubation for 30-60 min at 4°C cells are washed once with FACS buffer, resuspended in 100µl FACS buffer and binding of LINGO-1 specific antibodies is measured via FL2 fluorescence intensity of cells in FACSCalibur™ or FACSArray™ (Becton Dickinson).

For identification of LINGO-1 specific antibodies, stainings are done in parallel using CHO-K1-cmLINGO-1 or CHO-K1-rLINGO-1. Untransfected CHO-K1 cells serve as an additional control. Cynomolgus monkey and rat LINGO-1 expressing cells are chosen for screening as these species orthologues differ only in a few amino acids from the human LINGO-1 protein. Only those clones are judged as being LINGO-1 specific which are negative on untransfected CHO-K1 cells and ≥5x above background on LINGO-1 expressing cell lines. Cross-reactivity to human LINGO-1 and other orthologues (cynomolgus LINGO-1, rat LINGO-1) and to the human LINGO-2 paralogue is tested sequentially.
After sequence analysis thirty one (31) unique clones are identified that show strong binding to cell surface expressed human LINGO-1 in FACS analysis. Twelve (12) binders show strong binding to captured human LINGO-1-Fc in ELISA (signal:noise ratio greater than 10:1) and seven (7) show intermediate binding in ELISA (signal:noise ratio greater than 5:1). Four (4) of the binders showed strong binding to captured human NgR-Fc fusion protein (R&D Systems) in ELISA and are discontinued. Another three (3) of the binders do not cross-react to all of the three species of LINGO-1 and are discontinued. The remaining 24 clones that are cross-reactive to human/cynomolgus monkey/rat LINGO-1 but not to human NgR-Fc are expressed, purified and tested for their ability to significantly inhibit the binding of LINGO-1 to NgR (see Fig 1) and disinhibit the neurite outgrowth inhibitory activity of spinal cord myelin in vitro (see Figs 2-4) leading to the selection of Fabs 4784 and 4785 for further analysis. In an ELISA, 4784 and 4785 bind to captured human LINGO-1-Fc but no binding is observed to human LINGO-1-ΔLRR-Fc or human NgR-Fc compared to an unrelated Fc control (see Table 1 and Fig. 7). This indicates that 4784 and 4785 have epitopes that are within the LRR region (residues 66-353) of LINGO-1.

Table 1: Characterization of anti-LINGO-1 Fabs by ELISA

Human LINGO-1	Human LINGO-1 Fc	Human LINGO-1ΔLRR-Fc	Human NgR-Fc	Unrelated Fc
4784	98	49	68	52
4785	113	8	7	6

Values for ELISA analyses are given as mean values of relative fluorescence units.

Affinity Determination of selected anti-LINGO-1 Fabs using FACS saturation analysis

Cell based affinity of anti-LINGO-1 specific antibodies is determined by FACS saturation binding experiments. As the concentration of the antigen present in the sample to stain influences the apparent K_D values, only $1.25x10^4$ cells / well in contrast to $2x10^5$ cells / well are used in order to reduce the antigen concentration in FACS saturation experiments. Otherwise the staining procedure is done identical to the FACS staining procedure described above.

In detail, CHO-K1-hLINGO-1, CHO-K1-cmLINGO-1 or CHO-K1-rLINGO-1 are detached from culture flasks by versene, washed with FACS buffer and resuspended in FACS buffer. Purified anti-LINGO-1 Fabs are serially diluted in FACS buffer and spread into round bottom 96-well microtiter plates (NUNC™, Wiesbaden, Germany). For each concentration, duplicate wells are incubated with $1.25x10^4$ cells for 30-60 min on ice in a total volume of 100µl. After a washing step by applying 150µl FACS buffer and centrifugation for 5 min at 400xg, the cell pellets are resuspended in 100µl phycoerythrin-labeled secondary antibody (R-PE conjugated goat anti-human IgG (H+L) (Jackson ImmunoResearch) which has been diluted 1:200 in FACS buffer. After incubation for 30-60 min at 4°C cells are washed once with FACS buffer, resuspended in 100µl FACS buffer and binding of LINGO-1 specific antibodies is measured via FL2 fluorescence intensity of cells in FACSArray™ (Becton Dickinson). Apparent K_D values / EC50 values are determined from the saturation binding curves using GraphPad Prism v3.03 software or GraphPad Prism v4.03 applying a non-linear regression curve fit.

Using this assay the following apparent K_D values can be determined (Table 2). In Fab format the clone 4784 has rather weak affinities to human LINGO-1, cynomolgus monkey LINGO-1 and rat LINGO-1 (14.07nM, 27.11, and 24.03nM respectively). However, clone 4784 does not bind to human LINGO-2 in the Fab format. In Fab format the clone 4785 shows subnanomolar binding affinities (i.e. apparent K_D values being less than $1x10^{-9}$ M) to human LINGO-1, cynomolgus monkey LINGO-1 and rat LINGO-1. Clone 4785 shows cross-reactivity to human LINGO-2 in Fab format with low nanomolar to subnanomolar affinity. The consequence of cross-reactivity to LINGO-2 cannot be assessed at the time of writing as LINGO-2 function and distribution are as yet unknown. However, beneficial effects cannot be excluded.

Table 2: Apparent K_D values of anti-LINGO-1 Fabs to LINGO-1 or LINGO-2 expressed by CHO-K1 cells

	Human LINGO-1	Human LINGO-2	Cynomolgus LINGO-1	Rat LINGO-1
4784	14.07	nb	27.11	24.03
4785	0.35	1.21	0.26	0.260

Values given are mean values of apparent K_Ds in nM. nb, not binding.

Example 8: Cloning, expression and purification of HuCAL® IgG4

Conversion into the IgG Format

In order to express full length immunoglobulin (Ig), variable domain fragments of heavy (VH) and light chains (VL) are subcloned from the pMORPH®X9_MH (SEQ ID NO: 39) Fab expression vectors either into the pMORPH®_h_Ig (SEQ ID NOS: 40-42) or the pMORPH®2_h_Ig (SEQ ID NOS: 43-45) vector series for human IgG4.

Restriction enzymes EcoRI, MfeI, and BlpI a re used for subcloning of the VH domain fragment into pMORPH®_h_IgG4 (SEQ ID NO: 40): the vector backbone is generated by EcoRI / BlpI digestion and extraction of the 6400 bp fragment whereas the VH fragment (350 bp) is produced by digestion with MfeI and BlpI and subsequent purification. Vector and insert are ligated via compatible overhangs generated by the EcoRI and MfeI digests, respectively, and via the BlpI site. Thereby, both the EcoRI and the MfeI restriction site are destroyed.

Restriction enzymes MfeI and BlpI are used for subcloning of the VH domain fragment into pMORPH®2_h_IgG4 (SEQ ID NO: 43). In this new generation of IgG vectors, upon other modifications, the EcoRI site (which allowed only sub-cloning via compatible overhangs) is replaced by the MfeI site thus allowing MfeI / BlpI digestion of both, vector and insert.

Subcloning of the VL domain fragment into pMORPH®_h_Igκ (SEQ ID NO: 42) and pMORPH®2_h_Igκ (SEQ ID NO: 45) is performed via the EcoRV and BsiWI sites, whereas subcloning into pMORPH®_h_Igλ (SEQ ID NO: 41) and pMORPH®2_h_Igλ2 (SEQ ID NO: 43) is done using EcoRV and HpaI.

Transient Expression and Purification of Human IgG

HEK293 cells are transfected with an equimolar amount of IgG heavy and light chain expression vectors. On days 4 or 5 post-transfection the cell culture supernatant is harvested. After adjusting the pH of the supernatant to 8.0 and sterile filtration, the solution is subjected to standard protein A column chromatography (Poros 20A, PE Biosystems).

Example 9: Affinity Determination of selected anti-LINGO-1 IgG4s using FACS saturation analysis

Cell based affinity of anti-LINGO-1 specific antibodies is determined by FACS saturation binding experiments. The determination of the apparent K_D values is carried out identical to the procedure described above using anti-LINGO-1 Fab antibodies.

In detail, CHO-K1-hLINGO-1, CHO-K1-cmLINGO-1 or CHO-K1-rLINGO-1 are detached from culture flasks by versene, washed with FACS buffer and resuspended in FACS buffer. Purified anti-LINGO-1 IgG4s are serially diluted in FACS buffer and spread into round bottom 96-well microtiter plates (NUNC™, Wiesbaden, Germany). For each concentration, duplicate wells are incubated with $1.25x10^4$ cells for 30-60 min on ice in a total volume of 100µl. After a washing step by applying 150µl FACS buffer and centrifugation for 5 min at 400xg, the cell pellets are resuspended in 100µl phycoerythrin-labeled secondary antibody (R-PE conjugated goat anti-human IgG (H+L) (Jackson ImmunoResearch) which has been diluted 1:200 in FACS buffer. After incubation for 30-60 min at 4°C cells are washed once with FACS buffer, resuspended in 100µl FACS buffer and binding of LINGO-1 specific antibodies is measured via FL2 fluorescence intensity of cells in FACSArray™ (Becton Dickinson). Apparent K_D values / EC50 values are determined from the saturation binding curves using GraphPad Prism v3.03 software or GraphPad Prism v4.03 applying a non-linear regression curve fit. Using this assay the following apparent K_D values can be determined (Table 3).

The affinity of 4784 and 4785 IgG4 antibodies produced by using the pMORPH®2_h_Ig vector series are shown in Table 3. 4784 and 4785 in the IgG4 format have apparent K_D values clearly below 1 nM to human, cynomolgus and rat LINGO-1. 4784 has a far lower cross-reactivity to human LINGO-2 than 4785.

Table 3: Apparent K_D values of anti-LINGO-1 IgG4s to LINGO-1 or LINGO-2 expressed by CHO-K1 cells

	Human LINGO-1	Human LINGO-2	Cynomolgus LINGO-1	Rat LINGO-1
4784	0.29	25.94	0.62	0.98
4785	0.07	0.95	0.18	0.07

Values given are mean values of apparent K_Ds in nM.

Example 10: Influence of human Cerebro-spinal Fluid on Binding of selected anti-LINGO-1 IgG4s to human LINGO-1 using FACS analysis

Influence of human cerebro-spinal fluid on binding of anti-LINGO-1 IgG4s to human LINGO-1 is tested by FACS saturation binding experiments. Serial dilutions of the 4784 and 4785 are prepared. Binding to CHO-K1-hLINGO-1 is tested in the presence of 50% human cerebro-spinal fluid. The cells are stained in the presence of human CSF with these IgG4 antibodies according to the FACS stainings described above.

In detail, CHO-K1-hLINGO-1 are detached from culture flasks by versene, washed with FACS buffer and resuspended in FACS buffer. Purified anti-LINGO-1 IgG4s are serially diluted in FACS buffer plus 50% human serum and incubated for 60 min at 4°C. As controls, serial dilutions of the candidate binders in IgG4 format are incubated in FACS buffer with 2.6% BSA resembling protein content of human cerebro-spinal fluid for 60min at 4°C. After incubation the serial dilutions are spread into round bottom 96-well microtiter plates (NUNC™, Wiesbaden, Germany). For each concentration, duplicate wells are incubated with $1.25x10^4$ cells for 30-60 min on ice in a total volume of 100µl. After three washing steps by applying 150µl FACS buffer and centrifugation for 5 min at 400xg, the cell pellets are resuspended in 100µl phycoerythrin-labeled secondary antibody (R-PE conjugated goat anti-human IgG (H+L) (Jackson ImmunoResearch) which has been diluted 1:200 in FACS buffer. After incubation for 30-60 min at 4°C cells are washed once with FACS buffer, resuspended in 100µl FACS buffer and binding of LINGO-1 specific antibodies is measured via FL2 fluorescence intensity of cells in FACSArray™ (Becton Dickinson). Apparent K_D values / EC50 values are determined from the saturation binding curves using GraphPad Prism v3.03 software or GraphPad Prism v4.03 applying a non-linear regression curve fit.

Using this assay the influence of 50% human cerebrospinal fluid could be compared to the controls (Table 4). Incubation in 50% human cerebro-spinal fluid leads to a decrease in binding affinity with all binders being affected differently. The strongest impact on binding affinity by the presence of human cerebro-spinal fluid is seen for 4784 which shows a reduction in affinity by 73% from 0.43nM to 1.57nM.

Table 4: Influence of Human Cerebro-spinal Fluid on Apparent K_D values of anti-LINGO-1 IgG4s to LINGO-1 expressed by CHO-K1 cells

	App. K_D w/o 50% CSF	App. K_D w/ CSF	App. K_D ratio w/o CSF : w/ CSF
4784	0.43	1.57	0.27
4785	0.19	0.25	0.76

Values given are mean values of apparent K_Ds in nM.

Example 11: Influence of human Serum on Binding of selected anti-LINGO-1 IgG4s to human LINGO-1 using FACS analysis

Influence of human serum on binding of anti-LINGO-1 IgG4s to human LINGO-1 is tested by FACS saturation binding experiments. Serial dilutions of 4784 and 4785 are prepared in the presence of 50% v/v human serum. After incubation for 60 min cells are stained with these preincubated IgG4 antibodies according to the FACS stainings described above.
In detail, CHO-K1-hLINGO-1 are detached from culture flasks by versene, washed with FACS buffer and resuspended in FACS buffer. Purified anti-LINGO-1 IgG4s are serially diluted in FACS buffer plus 50% human serum and incubated for 60 min at 4°C. As controls, serial dilutions of the candidate binders in IgG4 format are incubated in FACS buffer plus 2.6% BSA resembling protein content of human serum or are incubated in FACS buffer alone for 60 min at 4°C. After incubation the serial dilutions are spread into round bottom 96-well microtiter plates (NUNC™, Wiesbaden, Germany). For each concentration, duplicate wells are incubated with $1.25x10^4$ cells for 30-60min on ice in a total volume of 100µl. After three washing steps by applying 150µl FACS buffer and centrifugation for 5 min at 400xg, the cell pellets are resuspended in 100µl phycoerythrin-labeled secondary antibody (R-PE conjugated goat anti-human IgG (H+L) (Jackson ImmunoResearch) which has been diluted 1:200 in FACS buffer. After incubation for 30-60 min at 4°C cells are washed once with

FACS buffer, resuspended in 100µl FACS buffer and binding of LINGO-1 specific antibodies is measured via FL2 fluorescence intensity of cells in FACSArray™ (Becton Dickinson). Apparent K_D values / EC50 values are determined from the saturation binding curves using GraphPad Prism v3.03 software or GraphPad Prism v4.03 applying a non-linear regression curve fit.

Using this assay the influence of preincubation in 50% human serum can be compared to the controls (Table 5). Incubation for 1hr in the presence of human serum has no effect on the K_D values of 4784 and 4785. These antibodies are therefore stable in human serum over this time period and, furthermore, as their K_D s are unchanged, they do not appear to cross-react with serum components.

Table 5: Influence of Human Serum on Apparent K_D values of anti-LINGO-1 IgG4s to LINGO-1 expressed by CHO-K1 cells

	FACS Buffer (FB)	FB + 2.6 % BSA	FB + 50 % HS
4784	0.28	0.19	0.27
4785	0.08	0.05	0.06

Values given are mean values of apparent K_Ds in nM.

List of Sequences with short description

SEQ ID NO: 1

Rat mature LINGO-1 ectodomain (residues 34-550)

TGCPPRCECSAQDRAVLCHRKRFVAVPEGIPTETRLLDLGKNRIKTLNQDEFASFPHLEE
LELNENIVSAVEPGAFNNLFNLRTLGLRSNRLKLIPLGVFTGLSNLTKLDISENKIVILL
DYMFQDLYNLKSLEVGDNDLVYISHRAFSGLNSLEQLTLEKCNLTSIPTEALSHLHGLIV
LRLRHLNINAIRDYSFKRLYRLKVLEISHWPYLDTMTPNCLYGLNLTSLSITHCNLTAVP
YLAVRHLVYLRFLNLSYNPIGTIEGSMLHELLRLQEIQLVGGQLAVVEPYAFRGLNYLRV
LNVSGNQLTTLEESAFHSVGNLETLILDSNPLACDCRLLWVFRRRWRLNFNRQQPTCATP
EFVQGKEFKDFPDVLLPNYFTCRRAHIRDRKAQQVFVDEGHTVQFVCRADGDPPPAILWL
SPRKHLVSAKSNGRLTVFPDGTLEVRYAQVQDNGTYLCIAANAGGNDSMPAHLHVRSYSP
DWPHQPNKTFAFISNQPGEGEANSTRATVPFPFDIKT

SEQ ID NO: 2

Cynomologus mature LINGO-1 ectodomain (residues 34-550)

TGCPPRCECSAQDRAVLCHRKRFVAVPEGIPTETRLLDLGKNRIKTLNQDEFASFPHLEE
LELNENIVSAVEPGAFNNLFNLRTLGLRSNRLKLIPLGVFTGLSNLTKLDISENKIVILL
DYMFQDLYNLKSLEVGDNDLVYISHRAFSGLNSLEQLTLEKCNLTSIPTEALSHLHGLIV
LRLRHLNINAIRDYSFKRLYRLKVLEISHWPYLDTMTPNCLYGLNLTSLSITHCNLTAVP
YLAVRHLVYLRFLNLSYNPISTIEGSMLHELLRLQEIQLVGGQLAMVEPYAFRGLNYLRV
LNVSGNQLTTLEESVFHSVGNLETLILDSNPLACDCRLLWVFRRRWRLNFNRQQPTCATP
EFVQGKEFKDFPDVLLPNYFTCRRARIRDRKAQQVFVDEGHTVQFVCRADGDPPPAILWL
SPRKHLVSAKSNGRLTVFPDGTLEVRYAQVQDNGTYLCIAANAGGNDSMPAHLHVRSYSP
DWPHQPNKTFAFIPNQPGEGEANSTRATVPFPFDIKT

SEQ ID NO: 3

Human mature LINGO-1 ectodomain (residues 34-550)

TGCPPRCECSAQDRAVLCHRKRFVAVPEGIPTETRLLDLGKNRIKTLNQDEFASFPHLEE
LELNENIVSAVEPGAFNNLFNLRTLGLRSNRLKLIPLGVFTGLSNLTKLDISENKIVILL

DYMFQDLYNLKSLEVGDNDLVYISHRAFSGLNSLEQLTLEKCNLTSIPTEALSHLHGLIV
LRLRHLNINAIRDYSFKRLYRLKVLEISHWPYLDTMTPNCLYGLNLTSLSITHCNLTAVP
YLAVRHLVYLRFLNLSYNPISTIEGSMLHELLRLQEIQLVGGQLAVVEPYAFRGLNYLRV
LNVSGNQLTTLEESVFHSVGNLETLILDSNPLACDCRLLWVFRRRWRLNFNRQQPTCATP
EFVQGKEFKDFPDVLLPNYFTCRRARIRDRKAQQVFVDEGHTVQFVCRADGDPPPAILWL
SPRKHLVSAKSNGRLTVFPDGTLEVRYAQVQDNGTYLCIAANAGGNDSMPAHLHVRSYSP
DWPHQPNKTFAFISNQPGEGEANSTRATVPFPFDIKT

SEQ ID NO: 4

4784 V_L

DIELTQPPSVSVAPGQTARISCSGDNIGNYYVYWYQQKPGQAPVLVIYEDTNRPSGIPERFSGSNSGNTATLTIS
GTQAEDEADYYCQSYDNLHEQVFGGGTKLTVLG

SEQ ID NO: 5

4784 V_H

QVQLKESGPALVKPTQTLTLTCTFSGFSLSSSGVGVGWIRQPPGKALEWLAHIGSDDDKYYSTSLKTRLTISKDT
SKNQVVLTMTNMDPVDTATYYCARNQQYGDGYPGYFDYWGQGTLVTVSS

SEQ ID NO: 6

4785 V_L

DIVLTQPPSVSGAPGQRVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLISRNSKRPSGVPDRFSGSKSGTSASLA
ITGLQSEDEADYYCSTYDTFSIVFGGGTKLTVLG

SEQ ID NO: 7

4785 V_H

QVQLQQSGPGLVKPSQTLSLTCAISGDSVSDNSAAWSWIRQSPGRGLEWLGLIYLRSKWDNDYAVSVKSRITINP
DTSKNQFSLQLNSVTPEDTAVYYCARTGRADEFDVWGQGTLVTVSS

SEQ ID NO: 8

DNA-4784 V_H

CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTTTCC
GGATTTAGCCTGTCTTCTTCTGGTGTTGGTGTGGGTTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGTGGCTG
GCTCATATCGGTTCTGATGATGATAAGTATTATAGCACCAGCCTGAAAACGCGTCTGACCATTAGCAAAGATACT
TCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTGCGCGCGTAAT
CAGCAGTATGGTGATGGTTATCCTGGTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

SEQ ID NO: 9

DNA-4785 V_H

CAGGTGCAATTGCAACAGTCTGGTCCGGGCCTGGTGAAACCGAGCCAAACCCTGAGCCTGACCTGTGCGATTTCC
GGAGATAGCGTGAGCGATAATTCTGCTGCTTGGTCTTGGATTCGCCAGTCTCCTGGGCGTGGCCTCGAGTGGCTG
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GATACTTCGAAAAACCAGTTTAGCCTGCAACTGAACAGCGTGACCCCGGAAGATACGGCCGTGTATTATTGCGCG
CGTACTGGTCGTGCTGATGAGTTTGATGTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

SEQ ID NO: 10

DNA-4784 V_L

GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGCGAT
AATATTGGTAATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATGAGGAT
ACTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACCATTAGC
GGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATAATCTTCATGAGCAGGTGTTTGGCGGC
GGCACGAAGTTAACCGTTCTTGGCCAG

SEQ ID NO: 11

DNA-4785 V_L

GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTGGCGCACCAGGTCAGCGTGTGACCATCTCGTGTAGCGGCAGC
AGCAGCAACATTGGTAATAATTATGTGTCTTGGTACCAGCAGTTGCCCGGGACGGCGCCGAAACTTCTGATTTCT
CGTAATTCTAAGCGTCCCTCAGGCGTGCCGGATCGTTTTAGCGGATCCAAAAGCGGCACCAGCGCGAGCCTTGCG
ATTACGGGCCTGCAAAGCGAAGACGAAGCGGATTATTATTGCTCTACTTATGATACTTTTTCTATTGTGTTTGGC
GGCGGCACGAAGTTAACCGTTCTTGGCCAG

SEQ ID NO: 12

Antibody 4784 CDR-H1
SSGVGVG

SEQ ID NO: 13
Antibody 4784 CDR-H2
HIGSDDDKYYSTSLKT

SEQ ID NO: 14
Antibody 4784 CDR-H3
NQQYGDGYPGYFDY

SEQ ID NO: 15
Antibody 4784 CDR-L1
SGDNIGNYYVY

SEQ ID NO: 16
Antibody 4784 CDR-L2
EDTNRPS

SEQ ID NO: 17
Antibody 4784 CDR-L3
QSYDNLHEQV

SEQ ID NO: 18
Antibody 4785 CDR'-H1
DNSAAWS

SEQ ID NO: 19
Antibody 4785 CDR'-H2
LIYLRSKWDNDYAVSVKS

SEQ ID NO: 20

Antibody 4785 CDR'-H3

TGRADEFDV

SEQ ID NO: 21

Antibody 4785 CDR'-L1

SGSSSNIGNNYVS

SEQ ID NO: 22

Antibody 4785 CDR'-L2

RNSKRPS

SEQ ID NO: 23

Antibody 4785 CDR'-L3

STYDTFSIV

SEQ ID NO: 24

Forward primer DM22

GGTTATCTCGAGACCGGCTGCCCGCCCC

SEQ ID NO: 25

Reverse primer DM23

GGCCCTTCTAGATCACTCGCCTGGCTGGTTGGAGATG

SEQ ID NO: 26

APtag-5-NHIS vector

gacggatcgggagatctcccgatcccctatggtcgactctcagtacaatctgctctgatgccgcatagttaagcc
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SEQ ID NO: 27

human LINGO-1 mature DNA sequence

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SEQ ID NO: 28

Cynomolgus monkey LINGO-1 mature DNA sequence

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SEQ ID NO: 29

Rat LINGO-1 mature DNA sequence

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SEQ ID NO: 30

Forward primer DM14

CTACGTCTAGAACGGGCTGCCCGCCCCGCT

SEQ ID NO: 31

Reverse primer DM15

GGTTTCTCGAGTCATATCATCTTCATGTTGAACTTGCGG

SEQ ID NO: 32

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SEQ ID NO: 33

Human LINGO-2 mature DNA sequence

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SEQ ID NO: 34

Forward primer DM16

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SEQ ID NO: 35

Reverse primer DM17

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SEQ ID NO: 36

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SEQ ID NO: 41

IgG Lambda Chain Expression Vector pMORPH®_h_Ig_lambda

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SEQ ID NO: 42

IgG Kappa Chain Expression Vector pMORPH®_h_Ig_kappa

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SEQ ID NO: 43

IgG4 Expression Vector pMORPH2®_h_Igγ4

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SEQ ID NO: 44

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SEQ ID NO: 45

IgG kappa Chain Expression Vector pMORPH®2_h_Ig_kappa

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CTGCGCCTTA TCCGGTAACT ATCGTCTTGA GTCCAACCCG GTAAGACACG
ACTTATCGCC ACTGGCAGCA GCCACTGGTA ACAGGATTAG CAGAGCGAGG
TATGTAGGCG GTGCTACAGA GTTCTTGAAG TGGTGGCCTA ACTACGGCTA
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TCGGAAAAAG AGTTGGTAGC TCTTGATCCG GCAAACAAAC CACCGCTGGT
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AAGTCTCCAC CCCATTGACG TCAATGGGAG TTTGTTTTGG CACCAAAATC
AACGGGACTT TCCAAAATGT CGTAACAACT CCGCCCCATT GACGCAAATG
GGCGGTAGGC GTGTACGGTG GGAGGTCTAT ATAAGCAGAG CTCTCTGGCT
AACTAGAGAA CCCACTGCTT ACTGGCTTAT CGAAAT

Claims:

1. A binding molecule which is capable of binding to the protein according to SEQ ID NO: 1, SEQ ID NO: 2, or SEQ ID NO: 3, with a dissociation constant <1000nM.

2. A binding molecule according to claim 1 which binds to one or more of the sequences chosen form the group consisting of; SEQ ID NO: 46-51.

3. A binding molecule according to claim 1 or 2 which is capable of disinhibiting spinal cord myelin at a concentration of less than 20nM.

4. A binding molecule according to claim 1, 2, or 3, which is capable of increasing the mean neurite length per cell of rat cerebellar granule cells grown on a substrate of adult rat spinal cord myelin by at least 20%.

5. A binding molecule according to any one of claims 1, 2, 3 or 4, which comprises one or more amino acid sequences chosen from the group consisting of SEQ ID NO: 12-17 or SEQ ID NO: 18-23.

6. A binding molecule according to claim 5, which comprises at least one antigen binding site chosen from the group consisting of;
   a sequence which is at least 50% homologous to SEQ ID NO: 5 or SEQ ID NO: 7, and;
   a sequence which is at least 50% homologous to SEQ ID NO: 4 or SEQ ID NO: 6, or a direct equivalent thereof.

7. A binding molecule according to claim 6, which comprises a first sequence which is at least 50% homologous to SEQ ID NO: 5 or SEQ ID NO: 7, and a second sequence which is at least 50% homologous to SEQ ID NO: 4 or SEQ ID NO: 6, or a direct equivalent thereof.

8. The binding molecule according to claims 1-7 which comprises at least
   a) one immunoglobulin heavy chain or fragment thereof which comprises
   (i) a variable domain comprising SEQ ID NO: 5 or SEQ ID NO: 7, and
   (ii) the constant part or fragment thereof of a human heavy chain; and
   b) one immunoglobulin light chain or fragment thereof which comprises
   (i) a variable domain comprising SEQ ID NO: 4 or SEQ ID NO: 6, and
   (ii) the constant part or fragment thereof of a human light chain; or
   direct equivalents thereof.

9. A binding molecule according to any one of claims 1-8, which is an antibody or a fragment thereof, or a direct equivalent thereof.

10. The binding molecule according to claim 9 in which the constant part or fragment thereof of the human heavy chain is of the γ4 type and the constant part or fragment thereof of the human light chain is of the κ type.

11. The binding molecule according to claims 1-9, which is a human or chimeric or humanized monoclonal antibody.

12. A polynucleotide encoding a binding molecule according to any one of claims 1-9.

13. A polynucleotide chosen from the group consisting of SEQ ID NO: 8 and SEQ ID NO: 9; or from the group consisting of SEQ ID NO: 10 and SEQ ID NO: 11.

14. An expression vector comprising one or more polynucleotides according to any one of claims 12 or 13.

15. An expression system comprising a polynucleotide according to any one of claims 12 or 13, wherein said expression system or part thereof is capable of producing a polypeptide of any one of claims 1 to 11, when said expression system or part thereof is present in a compatible host cell.

16. An isolated host cell which comprises an expression system according to claim 15.

17. The use of a binding molecule according to any one of claims 1 to 11 as a medicament.

18. The use of a binding molecule according to any one of claims 1 to 11 in the preparation of a medicament for the treatment of a CNS injury.

19. The use of a binding molecule according to any one of claims 1 to 11 in the treatment of a CNS injury.

20. A pharmaceutical composition comprising a binding molecule according to any one of claims 1 to 11 together with at least one pharmaceutically acceptable carrier or diluent.

21. A method of treatment of diseases associated with the promotion of axonal regeneration/plasticity comprising administering to a subject in need of such treatment an effective amount of a binding molecule according to any one of claims 1 to 11.